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Announcement

FORTHCOMING SYMPOSIUM NUMBERS, 1956

The Editors and Editorial Board plan, during 1956, three symposium numbers, each to occupy an entire issue of the JOURNAL. These Symposia, with their editors, authors, and tentative titles of the several articles, are as follows:

I. PAIN AND ITS RELIEF: Guest Editor, Louis C. Lasagna, M.D., Assistant Professor of Medicine and Assistant Professor of Pharmacology and Experimental Therapeutics, Johns Hopkins University School of Medicine.

Tentative date of publication—June, 1956.

1. *Introduction:* Louis C. Lasagna, M.D.
2. *Current Concepts of the Pain Process:* Frederick T. Haugen, M.D., Professor of Surgery, Head of Division of Anesthesiology, University of Oregon Medical School.
3. *The Case For and Against Experimentally Produced Pain:* Henry K. Beecher, M.D., Dorr Professor of Research in Anesthesiology, Harvard University Medical School.
4. *Experimental Pain in Man:* James D. Hardy, Ph.D., Professor of Physiology, University of Pennsylvania Medical School.
5. *The Usefulness of Laboratory Pain in the Study of Analgesics:* Stanley Harris, Ph.D., Professor of Physiology and Pharmacology, Northwestern University Dental School.
6. *The Search for New Analgesics:* Nathan B. Eddy, M.D., Secretary of the Committee on Drug Addiction and Narcotics, National Research Council.
7. *Surgical Pain: Therapy and Research:* Arthur S. Keats, M.D., Professor of Anesthesiology, Baylor University Medical School.
8. *The Management of Pain in Cancer Patients:* Henry M. Lemon, M.D., Associate Professor of Medicine, Boston University Medical School.
9. *The Control of Pain in Terminal Malignancy:* F.A.D. Alexander, M.D., Associate, Division of Anesthesiology, State University of Iowa Medical School.
10. *The Role of the Anesthesiologist in the Management of Pain:* James E. Eckenhoff, M.D., Professor of Anesthesiology, University of Pennsylvania Medical School.
11. *Addiction Problems in the Use of Analgesics:* Mark Rayport, M.D., Department of Neurology and Neurosurgery, Montreal Neurological Institute.

II. GLOMERULONEPHRITIS: Guest Editors, David P. Earle, M.D., Professor of Medicine, Northwestern University Medical School; and David Seegal, M.D., Professor of Medicine, College of Physicians and Surgeons, Columbia University.

Tentative date of publication—September or October, 1956.

1. *Introductory Statement:* David P. Earle, M.D., and David Seegal, M.D.
2. *Natural History of Glomerulonephritis:* David P. Earle, M.D., and David Seegal, M.D.
3. *Morphology of the Kidney in Glomerulonephritis:* William E. Ehrich, M.D., Professor of Histology, Professor of Pathology, Chairman of Department of Pathology, University of Pennsylvania Graduate School of Medicine.
4. *Microbiologic Considerations in Glomerulonephritis:* Charles H. Rammelkamp, M.D., Associate Professor of Preventive Medicine and Professor of Medicine, Western Reserve University School of Medicine.
5. *Immune Reactions in Human Glomerulonephritis:* Edward Fischel, M.D., Sc.D., Director, Department of Medicine, Bronx Hospital, New York, N. Y.
6. *Differential Diagnosis of Acute and Chronic Glomerulonephritis:* George Schreiner, M.D., Instructor in Medicine, Director Renal Service, Assistant Director Metabolism and Renal Service, Georgetown Hospital, Washington, D.C.
7. *Value of Renal Biopsy in the Diagnosis of Glomerulonephritis:* Robert M. Kark, M.D., Professor of Medicine, Illinois College of Medicine.
8. *Physiologic Aspects of Glomerulonephritis:* Saul J. Farber, M.D., Assistant Professor of Medicine, New York University College of Medicine.
9. *The Nephrotic Syndrome:* Henry Barnett, M.D., Professor and Chairman of Department of Pediatrics, Albert Einstein College of Medicine; and Henry Lauson, Ph.D., M.D., Professor of Physiology, Albert Einstein College of Medicine.
10. *The Management of Acute and Chronic Glomerulonephritis:* Thaddeus S. Danowski, M.D., Renziehausen Professor of Research Medicine, Pittsburgh School of Medicine.
11. *The Artificial Kidney in the Management of Glomerulonephritis:* John P. Merrill, M.D., Associate in Medicine, Harvard University Medical School.
12. *Kidney Transplants:* John P. Merrill, M.D.
13. *Experimental Glomerulonephritis:* Beatrice C. Seegal, M.D., Associate Professor of Bacteriology, College of Physicians and Surgeons, Columbia University; and Margaret Bevans, M.D., Associate Professor of Pathology, College of Physicians and Surgeons, Columbia University.

III. CORONARY HEART DISEASE: Guest Editor, Robert L. Levy, M.D., Professor Emeritus of Clinical Medicine, College of Physicians and Surgeons, Columbia University.

Tentative date of publication—November or December, 1956.

1. *Reflections on Anginal Pain and Cardiac Infarction:* Robert L. Levy, M.D.
2. *Cardiac Pain:* Tinsley R. Harrison, M.D., Professor of Medicine, Medical College of Alabama, University of Alabama; and T. Joseph Reeves, M.D., Associate Professor of Medicine, Medical College of Alabama, University of Alabama.

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3. *The Influence of a Hot and Humid Environment on the Patient With Coronary Heart Disease:* George E. Burch, M.D., Henderson Professor of Medicine, Tulane University School of Medicine.

4. *The Diet and the Development of Coronary Heart Disease:* Ancel Keys, Ph.D., Professor, School of Public Health, and Director of the Laboratory of Physiological Hygiene, University of Minnesota.

5. *Radioactive Iodine Therapy for Anginal Pain and Congestive Failure:* Herrman L. Blumgart, M.D., Professor of Medicine, Harvard University Medical School.

6. *Neurosurgical Methods for the Relief of Angina Pectoris:* James C. White, M.D., Professor of Surgery, Harvard University Medical School.

7. *Anticoagulants in the Treatment of Cardiac Infarction:* Stuart W. Cosgriff, M.D., Associate in Medicine, College of Physicians and Surgeons, Columbia University.

8. *Prognosis in Coronary Heart Disease:* David W. Richards, M.D., Clinical Fellow in Medicine, Massachusetts General Hospital, Trainee of the National Heart Institute; Edward F. Bland, M.D., Associate Clinical Professor of Medicine, Harvard University Medical School; and Paul D. White, M.D., Clinical Professor of Medicine, Emeritus, Harvard University Medical School.

9. *The Electrocardiogram and Vectorcardiogram in Coronary Heart Disease:* Charles E. Kossmann, M.D., Associate Professor of Medicine, New York University College of Medicine.

Original Communications

THE LIFE HISTORY OF THE NEURON

PAUL WEISS, PH.D., M.D. (HON.)

NEW YORK, N.Y.

From the Rockefeller Institute for Medical Research, New York

(Received for publication Nov. 3, 1955.)

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THERE was a time, not so long ago, when the life history of a neuron could have been described about as follows: A primitive cell, derived from the actively proliferating neural epithelium of the embryo, wanders off into the mantle, ceases to divide, enlarges, sprouts an axon, then dendrites, forms synaptic connections with other cells, neural or nonneural, enlarges further, receives end feet from other neurons, develops in quick succession a series of enzyme systems (see Flexner[7]), enlarges still more, deposits Nissl bodies in its cytoplasm; and, at last, is turned over to its user—the finished body—like a machine come off the assembly line essentially in ready working condition, just to be run in, polished, and improved in its wiring. This description, as you note, grants to the neuron, as to the machine, only a strictly limited epoch for its construction—called development—which in a standard mammal would occupy no more than about the first 1 per cent of the total life span. During the remaining 99 per cent, the owner would have to get along with the physical equipment previously received as a static and immutable apparatus. Once the embryonic assembly plant had been dismantled, no worn out parts could be replaced, no major repairs executed.

Evidently, this concept of a life history sharply divided into a formative and an operative phase has had a profound effect on our concept of aging. Machines, too, age, and principally from three causes: material decay—as when stone weathers or rubber rots; deposition of foreign matter—such as grit or sludge or slags; and ordinary wear-and-tear—which means the cumulative record of nicks and abrasions, accentuated by insults and negligence in use; all of these pointing

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to the scrap heap. Naturally, under the spell of this machine analogy, one has taken a similar fate of the neuron for granted. Partial to microscopic signs, one readily accepted certain insoluble pigment granules that pile up in ganglion cells with age, as visible evidence of such functional impairment.

Yet, more recent insight into the processes of development calls for a rather thorough reorientation of our thinking about such matters. Development is not compressed into a separate formative phase of life, but is coextensive with the whole life span, continuing from egg to death, even though with declining prominence; and since much of what we call aging is but a special aspect of development—the reverse side of the same coin—our concept of aging must be correspondingly adjusted. The notion of a neuron ever being truly completed, in the sense of a finished machine, is, as you shall see, an illusion. Development involves continuous transformations. Like other cells, live neurons can retain none of that precise, detailed, and durable stability of structure, equipment, and geometry that the printed stereotypes of our textbooks of microscopic anatomy have conjured in our minds. Of course, we all realize that no two cells, even of the same type, are ever nearly as much alike as are their five thousand identical illustrations in five thousand copies of the same textbook. But what we do not commonly realize is that not even any given cell is quite the same today as it was yesterday; indeed, it changes much more in one day than its textbook effigies have changed in many decades of transit from one text to another. The neuron is in perpetual flux of concurrent degradation and renewal. This instability renders it mutable, both in adaptive and regressive directions. And since this aspect of the life history of the neuron has much potential impact on problems of aging, I shall devote the substance of my further account to it.

That the neuron as a whole is not a stable, but rather a stationary, unit is a relatively recent discovery. There has been prior recognition of instability on the molecular level below, and of plasticity on the supracellular level above. On the molecular level, the extensive work with isotopes has revealed the unsuspectedly rapid turnover of protoplasmic constituents. On the supracellular level, those theories at least that try to refer phenomena of association, memory, and adaptive behavior to changes in the pattern of the neuronal network (or to modifications of interneuronal transmission) have had to discount the idea of a rigidly knitted set of relations between the neuronal elements. Yet, the neuron itself in between was still envisaged as a fixed body: a fixed harbor for a shifty population of active molecules, and a fixed element in the plastic web of connections. But now even this intermediate island of solidity has lost its former aspect of fixity. In this regard it falls in line with other protoplasmic systems in the body that are destined to last for life. In order that they may last, part of their protoplasm must remain reproductive so as to replace the constant drain on that other part which is either converted into specific functional products or just disintegrates in the normal course of catabolism.

To make this clear, let us briefly look at a column of skin reaching from the basal layer of the epidermis to its surface (Fig. 1, top). Normally only the cells at the base can grow and reproduce. They turn foodstuffs into more protoplasm of their own kind, and when they have grown to twice their size, they divide,

one cell retaining its basal position and reproductive function, while the other cell is pushed up one story. It soon is raised another story as the next cell is added from the base, while it in turn crowds the more outer cells. The column thus would keep on rising save for the fact that in their rise, the cells become progressively transformed into plain keratin, in which form they flake off the free surface. As long as the loss at one end and the gain at the other are equal, the column keeps a constant stationary height. Whenever production exceeds shedding, the height will grow, the skin become thicker; conversely, when shedding outstrips reproduction, the column will shrink.

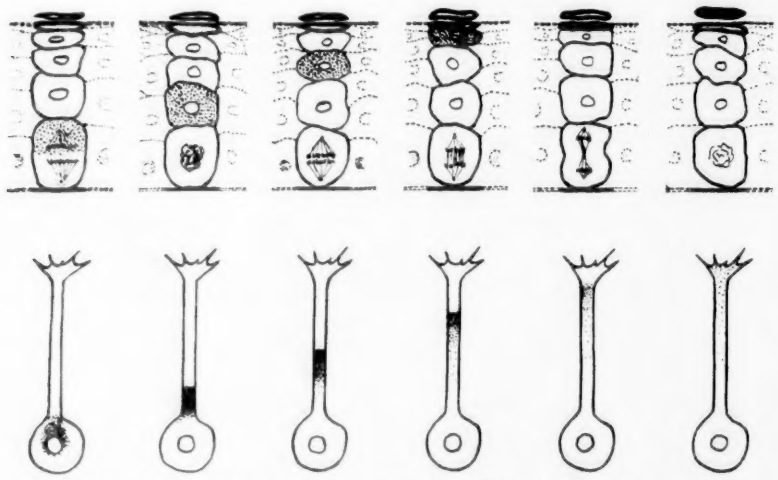

Fig. 1.—Diagrams of the mode of growth of a column of epidermis (top) and of a neuron (bottom). A newly produced mass of protoplasm (stippled) is followed through six progressive stages, from left to right, to its final disposal.

Now, but for the facts that in the skin the growing basal cells also divide and that the discard at the other end is visible, the column of skin cells is quite comparable to a single neuron, with the nucleated cell body, or perikaryon, corresponding to the base of the epidermal column (Fig. 1, bottom). For in the neuron, likewise, it is at this pole that protoplasm is continuously reproduced, then passed on to the rest of the neuron, where it is dissipated, albeit in molecular, hence less tangible, form. Just as in the skin column, the size of the neuron at any one moment, therefore, will only be an expression of the momentarily prevailing ratio of production over dissipation, and will remain constant only as long as the two opposing processes are in equilibrium.

Thus the difference between the steady state of skin, blood, and glands, on the one hand, and of neurons, on the other, is simply that in the former both loss and gain are grossly visible as cell destruction and cell division, respectively, whereas the neuron is less ostentatious. Just by a lucky accident did I discover microscopic signs of its perpetual growth. The diagram (Fig. 2) summarizes the results of six years' study, involving experiments and observations on more than one hundred thousand nerve fibers (Weiss and Hiscoe[24]).

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You see here nine mature neurons, a normal one on top, the others in various stages of ordinary or modified regeneration. The nucleated cell bodies are on the left, the periphery is on the right. Lines *B* to *E* recapitulate the regenerative events following the crushing of a fiber. The proximal stump issues a thin filamentous outgrowth, which advances through the distal degenerated portion into the periphery (as seen in *C*), where it makes connection with an old degenerated end organ, as in *D*. The new sprout is then still very thin. Only gradually does it enlarge in width, eventually approximating full caliber. To achieve this, it must grow in protoplasmic mass about a hundred fold.

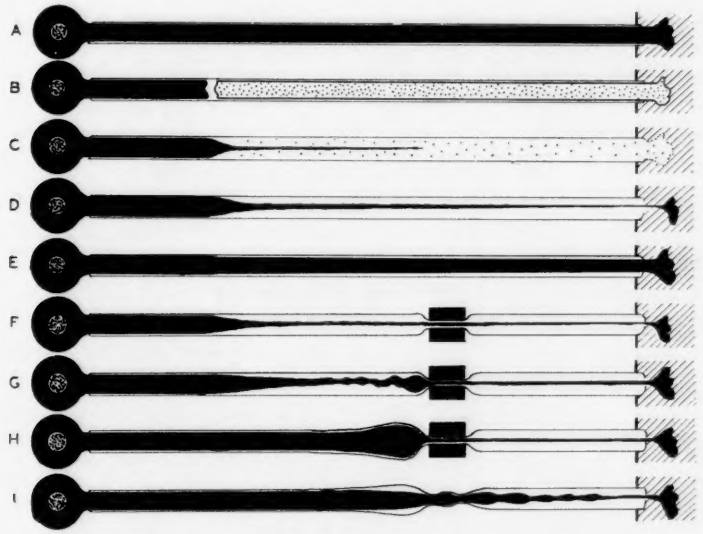

Fig. 2.—Diagrams of single nerve fibers in ordinary regeneration (*B-E*) and in regeneration combined with constriction (*F-I*), in the last case (*I*) followed by later release of the constriction.

It was this increase in girth which formed the subject of our investigations. By placing a constriction around a nerve, we can reduce the caliber of each constituent nerve fiber locally, as shown in lines *F*, *G*, and *H*. If now we cut the fiber proximally to the constriction, a thin filament again regenerates through the constriction (in *F*). But as this filament keeps enlarging and attains the diameter of the constricted portion, a marked asymmetry begins to appear between the portions of the fiber lying proximally and those distally of the constriction, as you can see in *G* and *H*. The distal portion remains thin, and permanently so; while at the proximal end of the constriction, surplus neuroplasm piles up. Conclusion: the growth of the axon evidently occurs solely from its base, and the constriction, acting as a bottleneck, has throttled the supply of growing mass to the distal portion.

Now, it is most important to understand precisely just how this growth occurs, and what it implies. In the first place, this is not simply a matter of pumping the distal fiber full of axonal substance, like distending a hose. If it were, the piece distal to the bottleneck would only take longer to attain full size, but eventually it would attain it. However, in reality, it never does: it stays forever nearly as thin as the bottleneck itself. It thus compares rather to a leaky hose being inflated. That is, its substance continues to suffer the drain of local metabolic consumption, while the replacement stream from the remote central source is slower in compensating for the loss because of the narrowed passage.

Second, while proximodistal convection of some prerequisites for axonal maintenance had indeed been postulated by Cook and Gerard[5] and by Parker and Paine,[16] this does not accurately express the situation. For what is conveyed from the cell to the axon is not a flux of essential supplements for local growth—for instance, enzymes for distal protein synthesis—but is a coherent column of finished axonal substance. As has been conclusively demonstrated by the qualitative and quantitative analysis of the configurations and deformations assumed by the axons at the central side of the constriction, the whole axon is in centrifugal motion.

The most dramatic evidence of this steady propulsion is obtained when the constriction is removed many months after the system has come to equilibrium. One can then directly follow the dammed-up protoplasmic surplus on the near side of the constriction forcing its way down through the widened passage, like a dammed-up stream through opened flood gates, on into the far portion of the fiber (see line *I* of diagram). The distal fiber segment of a constricted fiber may have been undersized for a year or more, and still resume larger caliber upon release of the stricture, as axoplasm can now enter with a broader front (Weiss and Cavanaugh[22]). Such a released axonal flood wave advances at the rate of several millimeters per day, which may be taken to be the order of magnitude with which the axonal column normally grows forth from its central base. If the liberation of ammonia from nerve is taken as a measure of the complete breakdown of protein in the peripheral portions, one would have to postulate a rate of replacement from the central supply source of the same order as that actually observed for the advance of the axonal column (Weiss and Hiscoe,[24] p. 370).

Finally, this axonal movement is by no means confined to phases of regenerative regrowth of a fiber, but is a permanent feature of neuronal life. For instance, if a partial constriction is placed on a full-sized mature nerve fiber without disrupting it, the distal part, though still connected with the cell body, gradually shrinks in accordance with the reduced entry of new axonal mass; it returns to its former dimensions whenever the obstruction is again removed.

What happens, evidently, is that new neuroplasm, produced continually in the nucleated territory of the cell, enters from there a sort of conveyor belt that moves it down into the periphery. On its way, it is then progressively consumed in the replacement of degrading protoplasmic systems, and the size of the neuron at any one time is simply a measure of the then prevailing ratio between over-all consumption and renewal from the central source. Thus, re-

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turning once more to the stationary column of epidermal cells (Fig. 1), we find it truly illustrative of the neuron, except for the fact that the latter does not divide and dissipates its substance diffusely, rather than in one terminal package.

More indirect confirmation of the continuous growth of the neuron has come from the cytochemical investigations of Hydén[12] and collaborators, who deduced a high rate of protein synthesis in the cell from the elevated nucleic acid concentration in and around the nucleus. Equally pertinent is the report from Gerard's laboratory (Samuels and associates[17]) that labeled phosphoprotein seems to shift peripherad in nerves at a rate of more than 2 mm. per day, which corresponds closely to the measured rate of axonal advance in our experiments.

After all this, the neuron now appears in a wholly new light. Divested of its simulated structural fixity, it assumes the wide latitude of adaptive expression open to a system in steady flux. Evidence for such adaptations, both of size and substance, is rapidly accumulating. Far from being set, size goes up or down with fluctuations in the rate of synthesis; the changes running parallel in cell body, nucleus, and nucleolus.

Thus far, only a few of the conditions governing the level of synthesis have been identified. One is the existence of peripheral connections. Unconnected neurons do not attain their full mass (Hydén[13]). A mature neuron, whose connections have been severed secondarily, undergoes a progressive reduction of dimensions, beginning with the nucleolus, speading to the nucleus, the cell body, and finally the diameter of the axon (Cavanaugh[4]), and chronic disconnection entails chronic undersize (Weiss, Edds, and Cavanaugh[23]; Aitken, Sharman, and Young[1]). When reconnected with a peripheral organ, the neuron gains again. If it is overloaded with additional branches and connections, its nucleus and cell body assume dimensions far in excess of normal (Edds[6]; Cavanaugh[4]). The production center of the neuronal mass thus conforms to the demands of the peripheral innervation volume.

Similarly, it adjusts itself to functional activity. Neurons chronically deprived of excitation tend to atrophy; conversely, nucleus and cell body enlarge in response to excessive functional bombardment. On the sensory side, this growth reaction has been observed in the cells of both the vestibular and cochlear ganglia (Hamberger and Hydén[9,10]). The marked early postnatal increase of relative mass in retinal cells presumably is also a functional effect of illumination, for it does not take place in the dark (Brattgård[2]). When the ganglion cells in the antidiuretic center in the hypothalamus are overactive in thirsting animals, their hyperfunction likewise entails enlargement of the nuclei and nucleoli (Ortmann[15]).

Our main point here is that because the neuron is not a settled fixture in the mechanical sense, because not only its interstices and surfaces, but the entire system is in a state of perpetual reorganization, its size remains greatly variable throughout life.

One could hardly assume that such wide fluctuations would leave unaffected the subtle connections of other neurons that end on the expanding or shrinking surface of the variable cell body. Just how the density and distribution of end feet and other relevant synaptic features would change, remains to be deter-

mined. But there can be little doubt that the relation between function and the size of the cell body is mutual; that not only does the cell body adapt its dimensions to the actual functional load, but that the resulting change of size will reciprocally affect some functional parameters.

To these quantitative changes must then be added the possibility of major qualitative adaptations to extraneous conditions, developmental, trophic, functional, or otherwise. Much of my early work, amply confirmed and expanded since by Sperry (see Weiss[20]), has clearly revealed that a neuron, switched to a different peripheral termination, can adopt the specific character and central response relations of its new end-organ. There is some evidence, though, that this adaptive faculty for qualitative modulation declines with advancing age (Weiss[18]); hence, its scope during later life is quite uncertain.

The biochemical basis of these qualitative modulations is much too subtle to be detectable by methods of current cytochemistry. However, those qualitative cytochemical changes that are directly demonstrable are, by their very grossness, indicative of the profound variability in its chemistry of which the neuron is capable. The well-known depletion of Nissl bodies during high activity has now been identified with a marked decreased of ribonucleic acids (Hydén[11]). At the same time, a conspicuous increase has been noted in the lipids of hyperactive ganglion cells (Purkinje cells of rabbits following prolonged rotation; Hydén[13]).

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Whatever all these changes may mean functionally, for us they signify that neuroplasm is subject to ceaseless change of composition throughout life. Let us examine what this implies.

The mechanisms of protoplasmic reproduction are still very obscure, but this much seems assured: (1) Gene replication is basically involved. (2) The complement of genes remains essentially the same in all cells of all somatic types. (3) Differentiation, on the other hand, connotes divergence of physical and chemical constitution in different cell types.

To reconcile this last fact with the thesis of gene constancy, one must assume that the extragenic protoplasmic systems of nucleus and cytoplasm assume divergent patterns, and that these latter then evoke different interactions from the same group of genes, or, as I have suggested, convert common gene products into cell-type specific compounds by serving as models or "templates" (Weiss[19 21]). In this way the cytoplasm can impose its pattern on substance newly procreated from genic sources in the nucleus. Accordingly, if the relevant molecular pattern in the cytoplasm undergoes changes, all subsequently reproduced mass would be cast into the changed mold, as it were, so that the changed configuration would be perpetuated.

Thus, as the neuron keeps renewing its substance, the pattern of this renewal may undergo significant alterations during life. Some of these changes may be of the slow autonomous kind often referred as to "maturation"; but there might also be others that are induced from the outside, comparable to the phenomenon of "adaptive enzymes." Many microorganisms can "learn" to metabolize unusual substrates and to pass this acquired faculty on to their offspring as long as the changed substrates are present (see Monod[14]). If this kind of self-per-

petuating modification were equally common in tissue cells, for which there is as yet no proof, then obviously the neuron, being in continuous self-reproduction, might perhaps be a case in point.

Let us now summarize. I have tried to show that the life history of the neuron cannot be written in static terms. It is a history of flux. What used to be viewed as stable *products*, has revealed itself as a steady flow of *production;* change in *equipment*, as a change in the *reproductive pattern*. Aging, therefore, would be not so much a matter of gain or loss of physical equipment, as a matter of inadequacies and incongruities arising in the renewal process, with the consequent decline of the adaptive features which that process sustains. If one insists on using a machine analogy, the machine that fails primarily in aging is not the physiologic machine which operates the nervous system, but the developmental machine which keeps that physiologic machine in good repair. The enormous complexity of the network of interactions essential for this process should caution us not to expect any one master reaction to hold the key to the understanding of neural aging. To add to the complexity, you must bear in mind that the life history of the neuron is, moreover, intimately connected with the life histories of the neuronal accessories, especially glia and sheath cells, which I have not even touched upon—largely because even less is known about them. Now, the resolution of complexity lies not in arbitrary simplification, but in the patient disentangling of the complex fabric. The threads I have tried to extricate here are but a modest few, yet they seem to lie close to the core of the perplexing problem of aging.

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THE CONTRIBUTION OF VOLUNTARY HEALTH INSURANCE

III. New Protection Against Major Expenses

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New York, N. Y.

(Received for publication Nov. 25, 1955.)

WHAT happens to 100 million Americans when their illness expenses go beyond the scope of the policies they have purchased to help defray hospital expenses? A new form of insurance—using the deductible approach and providing sums up to $5,000, $7,500, or even $10,000—appears to be the answer.

The two previous articles in this series have outlined the basic forms of health insurance which have become popular with the American public: cash benefits directed specifically against loss of income, hospital costs, surgical costs, and the calls of the general practitioner at home, in the office, or at the hospital. A wide variety of hospital, surgical, and medical expense policies is available to individuals from hundreds of companies.

However, the protection provided under these policies was not designed to meet the needs of those who are hospitalized for long periods, or of those whose surgical bills exceed the amounts provided in the schedules of surgical insurance policies. Nor were these policies designed to meet the expenses of those who require extensive treatment by medical specialists, or those who need special nursing care or expensive drugs outside the hospital. Although only a small percentage of people have such heavy expenses in a given year, such expenses can be financially disastrous for those who must pay them.

A NEW TYPE OF POLICY

To meet this need a different type of policy has been developed in the last few years. This new type of policy is known as major medical expense or health catastrophe insurance.

In general, major medical expense insurance not only goes beyond the usual policies and plans in protecting against heavy hospital and doctor bills, but it also protects against almost all other types of medical expense arising directly from the disability, including such costly items as special duty nursing expenses and charges for drugs. Moreover, major medical expense insurance ordinarily pays benefits whether hospitalization is involved or not.

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*Director of Health Insurance, Life Insurance Association of America, and Vice Chairman, Health Insurance Council. The Health Insurance Council is a confederation of insurance trade associations whose member companies are active in the sale of accident and health insurance: American Life Convention, American Mutual Alliance, Association of Casualty and Surety Companies, Association of Life Insurance Medical Directors, Bureau of Accident and Health Underwriters, Health and Accident Underwriters Conference, International Claim Association, Life Insurance Association of America, Life Insurers Conference.

This new coverage is popular. Born a little over five years ago, this new type of policy was held by two and one-half million Americans at the start of 1955. The chart (Fig. 1) shows the growth.

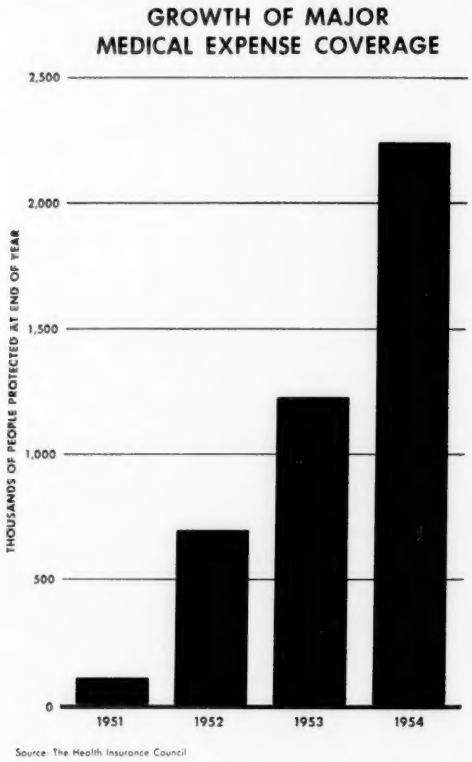

Fig. 1.

During the year 1955, half a million employees of the nation's railroads and also the employees of the General Electric Company have been among those purchasing this insurance for the first time. It is now estimated that the total numbers holding this form of insurance exceed four million persons including dependents.

Flexibility From the Point of View of the Providers of Services.—The flexibility of major medical expense insurance is of particular interest to physicians. Coverage is so broad, in most cases, that treatments not yet thought of will automatically be included. Just as medical practice has changed in the past decade, there is every likelihood that it will change in the next. Protection is available which will keep pace with changing times. This is accomplished by supplementing policies specially designed for hospital and surgical expenses and providing funds against the cost of *all* types of service needed to restore the individual to health. Substantially all types of medical expense, other than dental care, are included, though, as indicated later, mental and nervous diseases sometimes are subject to special provisions.

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Thus, the patient is free of financial pressure which might otherwise lead him to request hospitalization when such a course is not medically indicated.

This new insurance is not to be confused with so-called "dread disease" policies. Major medical expense insurance is designed to cover all diseases rather than a certain group of diseases. Heart disease, cancer, and poliomyelitis are included, as are the less spectacular but nonetheless serious diseases of the digestive tract.

Distinguishing Characteristics of Major Medical Expense Insurance.—This new form of insurance has three distinguishing characteristics: high maximum limits, a deductible feature, and a coinsurance clause.

In general, it may be said that the new policies provide a choice in maximum benefit limits of $2,500, $5,000, $7,500, or $10,000.

High maximum limits have for years been found in policies applying only in the case of accident. The new policies which cover both illnesses and accidents presented insurance companies with two problems of greater than normal financial impact. One was the frequency of minor illnesses. The other problem, which is explained later, was the subjective character of much illness as opposed to the objective character of an accident.

To meet these problems major medical expense policies generally contain two special features: a deductible provision and a coinsurance clause.

Eliminating the Small Claims: Deductibles.—A deductible provision, similar in nature to that found in most automobile collision policies, is utilized to eliminate not only small claims themselves but also the disproportionate administrative expense associated with them. It takes substantially as many claim forms, filled out by the physician and reviewed by the company, to process small claims as large ones. Although these small claims represent a large element of cost in the aggregate, minor bills can be readily taken care of by the insured and should be provided for by budgeting rather than through insurance. By excluding small bills from this new form of insurance, it is possible for the major medical premiums to remain at an attractively low level and for the insurance dollar to be used to best advantage in covering the larger elements of expense that can be such a hardship to the individual.

The deductible amounts commonly range from $50 to $500. The higher the deductible, the lower the premium. The policies generally provide that, in the case of a common accident affecting more than one insured person in the family, the deductible of only one of them shall apply to the combined expenses of those hurt in the accident.

Some insured persons want to take care of the smaller claims directly from their own funds, while others rely in part on the basic policies described in the previous articles to fill the gap. In working out the proper deductible for the particular case, it is desirable for both the prospective insured and the insurance company to take into account any basic benefits previously purchased. Otherwise, in certain claim situations the insured would be paying for and receiving double benefits, thus destroying the principle of the deductible. Group insurance contracts frequently require that the insured employee incur an "out-of-

pocket" deductible exclusive of the basic benefits and before the application of the major medical expense benefits.

As a new form of insurance develops, there is frequently some difference of opinion among insurance experts concerning the best method of proceeding. Each new form is an experiment and, until the collective experience of the companies becomes significant, varied approaches to the problem of the deductible are used.

For example, there is some difference of opinion between those who believe that the deductible should be geared to each separate illness or period of disability, and those who believe that there should be a calendar year deductible per person. From the point of view of the patient, there is this difference. If the deductible is "per illness," then the $50, or $100, or $300, or $500 is deducted only once even though the illness lasts beyond the first year. If the deductible is "per year," then it is reapplied each year even on the same illness, but separate illnesses in the same year are subject to only the one deductible.

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Actually, the true difference between these two approaches to the deductible may never be learned because most of the "per illness" deductible plans require that after two or three years the claimant must meet a new deductible for the same illness. With some companies, benefits cease entirely after the two- or three-year period, whereas with others the remainder of the maximum continues to be available for the particular illness, subject to the reapplication of the deductible.

Subjective Nature of Illness: Coinsurance.—The provision in this new type of policy of rather large aggregate amounts, running as high as $10,000, brings into focus more clearly than ever before the subjective character of many illnesses. To deal with this, the companies find it necessary to make very specific provisions with respect to coinsurance.

Probably every physician knows of cases where one person is so sick that he thinks he should go to the hospital, while another, with the same condition physically, thinks he is well enough to go to work. The different reactions to the same situation are affected, not only by an individual's impression of his own sickness but also by such things as his previous relations with his physician, his present relations with his family and his employer, and his financial situation.

These reactions of individual patients may result in unwarranted demands upon both the physician and the hospital. The physician may be asked to spend unnecessary time on fancied illnesses, thus reducing the time he has available for really sick people.

Financial worries can contribute to illness and retard recovery; on the other hand, the certainty that treatment is available without substantial expense may encourge a person to seek unnecessary treatment or prolong treatment. While it is undesirable that lack of money should prevent proper treatment, it must be remembered that unnecessary treatment for many people, due to the presence of insurance, will increase the cost of the insurance, possibly to the point where it would be a heavy burden for people to buy it.

The companies have tried to solve this dilemma by introducing a financial sharing on the part of the patient, known as "coinsurance." Once the expenses

go above the amount of the deductible, be it $50, or $100, or $300, or $500, the patient pays from his own funds a percentage of each additional dollar spent for his medical care. Generally the insurance company's share above the deductible is limited to 75 per cent of the expenses, with the patient paying the remaining 25 per cent. The patient thus has a direct financial interest in each dollar of medical or hospital care ordered for him.

How Major Medical Insurance Works in a Typical Case.—As an example of the way major medical insurance works, take the case of G. W., a married man with two children, earning $6,500 a year as a machine shop foreman. When he developed a brain tumor, his family doctor recommended one of the best brain specialists in the state. The resulting expenses amounted to $3,406.95, as shown in Table I.

TABLE I. THE APPLICATION OF MAJOR MEDICAL INSURANCE TO A TYPICAL CASE (see text)

	TOTAL EXPENSES	EXPENSES PAID BY BASIC PLAN	COVERED EXPENSES UNDER MAJOR MEDICAL PLAN
Expenses in the Hospital			
Hospital room and board—45 days at $15	$ 675.00	$450.00	$ 225.00
Other hospital charges	717.95	150.00	567.95
Surgeon's fee for brain operations (2)	1,200.00	300.00	900.00
Ambulance to and from the hospital	30.00		30.00
Registered nurses (3 shifts for 14 days)	504.00		504.00
Expenses Outside the Hospital			
Medical consultation fees	100.00		100.00
Special x-ray studies	75.00		75.00
Postoperative medical care	60.00		60.00
Drugs and medicines while convalescing	45.00		45.00
	$3,406.95	$900.00	$2,506.95

Major Medical Expense Benefits Paid as Follows:		
Expenses not paid by basic plan		$2,506.95
Less deductible—paid by Mr. W.		100.00
Balance		$2,406.95
Paid by major medical expense plan—75%		1,805.21
Paid by Mr. W.—25%		$ 601.74

Summary

		AMOUNT	PERCENTAGE OF TOTAL
Total expense		$3,406.95	100
Paid by basic plan	$ 900.00		26.4
Paid by major medical expense plan	1,805.21		53.0
Total paid by insurance	$2,705.21	2,705.21	79.4
Paid by Mr. W. (including $100 deductible)		$ 701.74	20.6

Without his insurance, these expenses would have wiped out his savings and put him deeply into debt. For, out of his $450 monthly take-home pay, nearly $375 goes for food, clothing, housing, and those taxes and insurance premiums which are not withheld from his wages. Payments on his automobile and various small luxuries use up a large part of the remainder. Still, over a period of years, he had accumulated savings of $1,000, so that, having major medical insurance, he did not have to give up his car or borrow on his life insurance.

Mr. W. has subscribed to basic hospital and surgical expense insurance, and more recently to major medical expense insurance. All three policies are group policies bought through his employer. Because the employer pays part of the cost, his premiums, for himself, his wife, and his children, amount to only $8.00 per month.

The basic plan paid $10.00 a day toward his hospital room and board bill of $15 a day, and $150 toward the additional hospital charges of over $700. It paid $300 of the surgeon's $1,200 bill. The remaining expenses, including in-hospital expenses not covered by the basic plan and other expenses incurred outside the hospital, were eligible for consideration under the major medical plan, subject to $100 deductible and 25 per cent coinsurance. Thus, the basic policies paid $900 and the major medical expense policy paid twice this amount, for a grand total of $2,700 in insurance payments against a $3,400 total bill.

Mr. W.'s situation is being repeated each day as claims begin to come through under major medical expense policies. Physicians will be interested in the payment experience under two group policies where the insurance company in question has classified the claims by broad categories of diagnoses (Table II).

TABLE II

DIAGNOSIS	NUMBER OF CASES	PER CENT OF THIS DISEASE IN TOTAL NUMBER	AVERAGE TOTAL ELIGIBLE CHARGE FOR THIS DISEASE
Digestive disorders	147	25	$ 918
Genitourinary	129	22	863
Brain and nervous	50	9	947
Circulatory	48	8	1035
Accidents	34	6	1517
Respiratory	27	5	722
Glandular	25	4	1352
Maternity	17	3	487
Other	106	18	865
Total	583	100	$ 940

One insurance company reports that in 318 costly situations, where both the basic benefits and the major medical expense insurance were present, the insurance company's share of the cost has been raised on the average from 48 per cent to 82 per cent.

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HOW MAJOR MEDICAL EXPENSE INSURANCE IS SOLD

It is one thing to design a satisfactory policy, but quite another problem arises in popularizing it. Fig. I shows unusual growth. How varied is the acceptance of this new product by diverse elements in the population?

A. Insurance Offered to Individuals.—The experience of one company active in the sale of this new coverage is described as follows:

> We felt from the outset that the need for this protection was widespread and we are, therefore, gratified to find our sales distributed throughout the country. There is little concentration in big cities: many sales are being made in small communities and rural areas. A sample of our issues shows a wide range of occupations represented, including doctors, lawyers, accountants, professors, salesmen, insurance agents, students, housewives, and skilled workmen.

A recent review of major medical expense insurance, sold to individuals as distinct from groups, was made by one of the member associations in the Health Insurance Council. Because of the newness of this field of insurance, it is not possible to pick a typical policy, but the particular experience of certain companies will give some indication of the general trend.

In the case of one company, for example, about half the applicants selected the $2,500 maximum and about half the $5,000. It was found that applicants choosing the lower maximum ($2,500) also most frequently chose the lowest deductible ($100). Only 34 per cent of those selecting the $5,000 maximum chose the $100 deductible. This group of applicants leaned more toward the $500 deductible than the first group.

Some companies require that applicants in higher income brackets select the higher deductible.

One company found that about half of the policyholders are in the income group from $4,000 to $12,000, with the rest distributed both above and below these levels.

As illustrated by Table III, there are substantial numbers of family members covered.

TABLE III

	COMPANY "A"	COMPANY "B"	COMPANY "C"	COMPANY "D"
Distribution by				
Family	84%	70%	71.2%	74%
Individual	16%	30%	28.8%	26%

The average number of persons per family unit was approximately three.

Pre-existing conditions are usually excluded from the coverage under all forms of individual insurance because this merchandising method does not furnish the broad cross section of risk available in group underwriting. An interesting departure from tradition has been taken by some companies which do not incorporate a general exclusion of health conditions existing at the time the insurance is purchased. In such instances, care must be taken, of course, to see

that those insured are in fact in good health at the time the policy is issued. The company may exclude by a rider attached to the policy only the specific condition of the applicant which makes him a substandard risk. This same technique can be used to exclude an uninsurable dependent, thus making it possible for the rest of the family to be insured.

Of 19 companies surveyed, the greatest number will offer policies to applicants up to age 55 or older. One company reports that the average age of its major medical expense policyholders is 41 years.

Most companies will continue to renew these policies to age 64 or 65, if a reason for cancellation does not appear in the interim. One company issues a guaranteed renewable policy for life, but with less benefits available after age 65 than prior thereto. Some companies follow a middle course of not exercising their rights of cancellation where the sole reason for doing so is the deterioration of health of the insured.

Normal exclusions in individual policies are mental and nervous disorders (by and large functional rather than organic); maternity (except unusual complications); dentistry (except as may be required as the result of accident); the cost of confinement in a hospital which does not normally render bills (such as the Veterans Hospitals); expenses arising as a result of war and the care of persons in the Armed Forces; job-connected injuries (already paid for under Workmen's Compensation Insurance).

Almost half of the companies surveyed are not now excluding mental and nervous disorders, although some require that the expenses in such a case be incurred in a general hospital.

The inclusion of the ordinary expenses of maternity under the basic policies rather than under the major medical policy is a good example of the purpose of major medical expense insurance. The maternity expenses are relatively uniform and relatively minor, and can be anticipated in family budgeting for several months prior to delivery.

There are approximately 50 companies offering major medical expense insurance to individuals.

B. *Insurance Offered to Groups.*—Most of the major medical insurance sold thus far has been sold to groups. These group policies may be of a conventional sort, purchased by a single employer for his employees; or they may be industry-wide groups, under which an association of employers or a union is the contract holder. Through this latter method, many employers, too small to qualify for group insurance on their own, may join with other small employers in the same line of business in providing funds for group benefits.

One of the large companies writing group insurance reports that the distribution of persons covered under their groups is as follows:

63 Groups—less than 100 employees
35 Groups—between 100 and 500 employees
7 Groups—between 500 and 1,000 employees
5 Groups—over 1,000 employees

All but four group cases cover dependents and in the 106 groups there are approximately 100,000 dependents.

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As indicated, group insurance can be broader in some of its provisions because it is possible through the group approach to obtain a broader cross section of risk. Thus, employees, if actively at work and willing to subscribe at the time the coverage is first offered to them, are covered regardless of existing medical conditions; and dependents are likewise covered unless they are in the hospital or are undergoing treatment.

In addition, group insurance is cheaper because it is sold by the mass merchandising method and the employer collects the employee's share of the premium through payroll deduction. The employer's share of the premium is itself a most important factor in reducing the cost to the individual. One company reports:

> Approximately 28% of our cases are on an employee-pay-all basis, 22% involve an employer contribution to the premium of less than 50%, and 50% involve an employer contribution of 50% or more of the premium.

In group insurance, the executives were the first level of employees who were interested in purchasing major medical expense coverage. More recently, there has been a trend toward major medical for all employees. One insurance company reports that 80 per cent of their groups are "total groups" in that they run from low to high in the income scale.

Sometimes salaried employees, as distinct from union employees, are covered. Sometimes entire unions, operating under welfare plans, cover their membership which works for hundreds of employers in the same industry. The new form of coverage is becoming an accepted part of the bargaining process for employee benefits. In fact, the deductible in a large group case is frequently expressed as a percentage of the employee's wages rather than as a specified sum of money. Another effect of union bargaining has been to reduce the deductible to $50 in some cases.

The exclusions under group insurance are about the same as under individual insurance except that expenses of mental and nervous disorders are generally as eligible for reimbursement under group insurance as any other type of illness. Some plans, particularly when requested by an employer buying the coverage, are written so as to increase the employee's coinsurance share of the expenses in diseases of this character from 25 per cent to 50 per cent. The employer may make this request on the ground that nervous and mental disorders are in many cases quite subjective, and it is unfair to load on either the employer or the fellow employees the cost of psychiatric treatments obtainable on a continuous basis "after hours."

Today, most companies selling group insurance offer major medical expense insurance to their normal clientele.

HOW IS THE COST OF MAJOR MEDICAL INSURANCE DETERMINED?

As indicated, group insurance is cheaper than insurance purchased individually for much the same reason as pertains to any product merchandised by wholesale rather than retail methods. It is also apparent that the cost to the individual of group insurance will vary widely with the extent of the employer's

contribution to the premium cost. In addition, most insurance premiums are a direct reflection of claim costs. If claims move upward, premiums are bound to follow this trend. Conversely, some companies writing individual policies anticipate paying dividends if claim experience is satisfactory. Thus, initial premium charges may turn out to be in the nature of gross costs with lower net costs later developing. This is particularly true under group insurance, where employers expect to receive dividends or experience rating credits after a period of favorable operation, thus reducing the gross cost.

What is not so apparent is that even the gross premium for a group may vary in accordance with other factors. While it is not always possible to reflect these other factors in the initial premium rate, it should be noted that:

1. The cost of major medical expense insurance varies directly with the income of those insured: if it is restricted to an executive group, the cost will be higher because higher groups are often charged for medical treatment in accordance with ability to pay.
2. The cost increases with age in much the same way as the mortality curve does, with the cost at age 65 being roughly ten times that at age 35.
3. The cost varies with the geographic area, since physicians' fees and hospital charges tend to follow economic levels, area by area.
4. The cost will vary with the structure of the plan: the amount of the deductible, the proportion of coinsurance and the nature of the basic benefits if any. If the basic plan benefits are high, the basic plan will carry more of the cost load.
5. There is what we might call approximately a 1-2-3 cost among members of the family. If the employee's claim cost is represented by two, his wife's is three, and his dependent children as a unit, only one.
6. In group insurance the cost will be higher if a disproportionate number of the employees are females.

Many of these factors, of course, are equally true of individuals not associated with groups. However, some feel it is not practical to take into account more than age and family factors when setting rates for individual insurance. The premiums of individual companies vary, both because of normal competitive conditions and because of the uncertainty of a new field.

As one company official remarked:

> The absence of statistics or precedent, on the basis of which to construct premium rates, establish policy provisions, and to develop administrative procedures, made this a pioneering venture, indeed.

HOW THE MEDICAL PROFESSION MAY ASSIST

One of the main points made by advocates of Federal compulsory health insurance has been about the gaps in voluntary health insurance coverage. It is to the advantage of both medicine and insurance that significant gaps be closed. All types of voluntary health insurance are a contribution to this objective. Major medical expense insurance, because it goes far beyond hospitalization and surgical insurance, is especially important in the joint effort.

To assure success, two subsidiary objectives must be reached. The first is that the cost of the new insurance must be kept within the reach of the buying public, and the second is the need for public education about this new form of insurance.

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To reach the first objective, it is important to realize that insurance neither multiplies dollars nor reduces aggregate costs. Thus, physicians should not regard the presence of this insurance as increasing the public's "ability to pay," *but rather should recognize that insurance is a convenient method of spreading costs among self-supporting individuals, and that any aggregate increase in costs for the whole insured population will merely be reflected in increased premium rates.*

This is not to say that increased usage of medical facilities or increased costs due to more effective but more expensive medical procedures is not desirable. One of the reasons for developing all forms of health insurance was to remove the fear of the financial consequences of a serious illness and thus encourage the prospective patient to seek early preventive care. Nor is the attainment of this objective meant to deny to physicians, and to other providers of services in the health field, a normal up-grading of income along with the rest of the population in inflationary times. Rather, it is an expression of confidence, based on past experience, that fees and charges will not rise just because of the presence of the insurance.

To reach the second objective, it is necessary to let the public know about the availability of this new form of coverage, together with an understanding of how it works. The need for budgeting the small costs and linking this budget amount with operation of the deductible feature of major medical expense insurance must be understood. Because of the respect with which individual physicians are regarded in their several communities, they are ideally suited to assist in this educational effort.

It is interesting to speculate on the future of this particular type of insurance. As indicated in previous articles, the conventional forms of insurance which have proved so popular over the last two decades are benefiting large numbers of people. Over 100 million persons have some form of hospitalization insurance, and close to 90 million persons have surgical insurance. Will these policies in time be completely replaced by policies carrying a low deductible—for example, $25.00, with the coinsurance factor being applied to all expenses above that amount? There are already indications in the field of group insurance that this has appeal to employers and employees alike. During the next decade insurance experts will be called upon to re-examine insurance coverages which devote a disproportionate part of the premium dollar to small claims. Perhaps, as we grow in our experience, we will all have the satisfaction of seeing voluntary health insurance fulfil its original purpose, which is: providing timely benefits in sufficient amount to prevent the cost of ill health or accident from spelling financial hardship to individuals and families who might otherwise suffer such hardship.

HERITABLE DISORDERS OF CONNECTIVE TISSUE

VII. The Hurler Syndrome

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HISTORICAL NOTE

THE disorder which is now called, among other names, the Hurler syndrome, is said by Henderson[48] to have been recognized by John Thomson of Edinburgh about 1900. The first definitive description was that of Charles H. Hunter* whose report appeared in the *Proceedings of the Royal Society of Medicine* in 1917 while he was serving in England as a major in the Canadian Army Medical Corps. This beautifully detailed and descriptive report concerned two brothers, aged 10 and 8 years, respectively, who were admitted to the Winnipeg General Hospital in 1915. The habitus was typically dwarfed. There were deafness, widely spaced teeth, short neck, protuberant abdomen with hepatosplenomegaly, inguinal hernias, short, broad, thick, stiff hands, semiflexed knees, noisy respiration. The elder boy had cardiomegaly and "a distinct diastolic murmur audible in the third and fourth left interspaces close to the sternum . . . ; at the apex, a systolic murmur was conducted towards the axilla." Twelve illustrations, including many x-rays demonstrating typical changes (such as "shoe-shaped" sella), were presented by Hunter. The boys appeared to be normally intelligent; clouding of the cornea was not observed; the spine was straight with loss of the normal contour but there was no gibbus.

In 1919 Gertrud Hurler of Munich[56] published cases at the suggestion of Professor Meinhard von Pfaundler,[88] who was chief of the University Clinic of Pediatrics and who had presented two patients with this syndrome to the Munich Society for Pediatrics on June 27 of the same year. The patients of Hurler and Pfaundler were infants; gibbus was present, as were corneal clouding and retardation of intellect.

It is surprising that Hunter's beautiful publication received, compared to Hurler's, relatively little attention. Subsequently, even in the English-speaking medical world, it was principally Hurler's paper which was referred to

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Reprints of this entire series of articles, appearing in successive issues of the Journal, will be available through the publishers in book form following appearance of the last installment.—Editor.

*Hunter was later Professor of Medicine in the University of Manitoba, Winnipeg. He died March 18, 1955, at the age of 82 years (Canad. M. A. J. **72**:712, 1955).

and the names of Hurler and Pfaundler which became most firmly associated with the syndrome. (A similar situation exists in connection with the Morquio syndrome which was described in England by Brailsford slightly earlier than by Morquio of Montevideo.)

The nosography of the Hurler syndrome has now advanced to the point where the limits of the syndrome and its several clinical and pathologic features are reasonably well described, although mildly affected persons are still difficult to identify with certainty. A tabular survey of a large portion of the reported cases has been presented by Jervis.[63] Emanuel[36] estimated that over 200 cases had been reported by 1954.

Many different names have been suggested for this syndrome. Husler[57] suggested "dysostosis multiplex." Ellis and his co-workers,[34] Cockayne[17] and other English authors used the term gargoylism.* Washington[117] suggested lipochondrodystrophy, believing this to be a disorder of lipid metabolism. This is the term used by the *Cumulative Index Medicus*. However, it is probably a misnomer, as indicated by recent evidence bearing on the basic defect of the disease (see below). This is another instance demonstrating the desirability of using noncommittal terms in connection with these syndromes in which the basic defect is as yet unknown. Consistent with my practice with other syndromes discussed in this series, *the Hurler syndrome* is the designation which has been used here. Equally acceptable are the names of Pfaundler and of Hunter, which are sometimes associated with this condition.

In spite of Hunter's claim to priority, Hurler's name is selected for use because it is the eponym most firmly established in the literature. It is, after all, merely a symbol to indicate a clinical syndrome which is incompletely understood. Although there is some suggestion that what Hunter and Hurler described were genetically and clinically distinct entities (*v. seq.*), it is preferable to consider all these cases one syndrome, the Hurler syndrome, until the basic defect is more accurately known and methods for distinguishing precisely the possible subgroups of the syndrome are available.

Recently, Brante[11] has classified the Hurler syndrome as a mucopolysaccharidosis, and Uzman[113] has presented evidence that the defect is one of "structural polysaccharide." The development of views about the basic nature of this disease are discussed below in the section dealing with that particular aspect.

CLINICAL MANIFESTATIONS

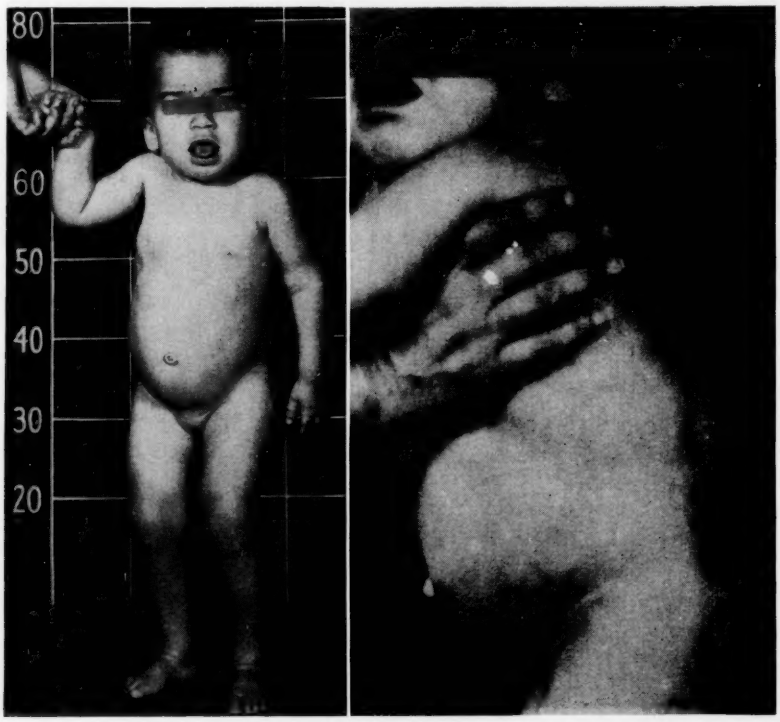
The clinical description provided here is based on the findings in sixteen patients with the Hurler syndrome seen at this hospital and at the Rosewood State Training School.

The cardinal features of this syndrome are disproportionate dwarfism with a characteristic, grotesque skeletal deformity, limitation of joint motion, deafness, hepatosplenomegaly, cardiac abnormality (either from the outset or developing

*This seems an unnecessarily cruel term in view of the fact that the intellect may be little impaired and survival to adulthood is not infrequent. It is scarcely a diagnosis which can be cited to a parent, for example. Families sometimes raised legitimate objections to such statements (all too frequent in the literature) as these: "He is a typical gargoyle"; "there are three gargoyles in this family."

with the passage of years), clouding of the cornea, and mental retardation. The last two features need not be present.

The patient frequently appears normal at birth but, with the passage of the first year (a "symptom-free interval"), becomes manifestly abnormal. The lines along which development occurs in these patients is so similar from patient to patient that, as in the Marfan syndrome, myotonic dystrophy, Mongolism, and other conditions, the patients, even though unrelated, tend to resemble each other more than their unaffected siblings.



A. *B.*

Fig. 1.—Thirty-four-month-old child (S. S., B3747). The child is mentally retarded. The liver and spleen are enlarged, the corneas cloudy, and the teeth short, abnormally formed and late in appearing. The fingers show flexion contractures as do other joints to a slight extent. There is constant nasal congestion so that the patient is a mouth-breather. Most of these features are evident in *A*. In *B* the lower dorsal, upper lumbar gibbus is evident. The skeletal basis for this appearance is shown by the x-ray of the spine in *C*. Note the lumbar kyphos, beaking of the lumbar vertebrae, the sabre-shaped ribs, hepatosplenomegaly.

The head is large and bulging, often with prominent scalp veins in the case of small children. The bridge of the nose is flattened, creating a saddle appearance. Hypertelorism is usual. The skull is often scaphocephalic,* i.e., shaped like the keel of a boat, seemingly as a result of premature closure of the sagittal and metopic sutures with hyperostosis in those areas. This hyper-

*There is usually no difficulty in distinguishing the Hurler syndrome from the specific conditions given the generic names *acrocephaly* and *scaphocephaly*,[87] although in the earlier days of the nosography of Hurler's syndrome such confusion did occur.[61]

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ostosis often creates a longitudinal (sagittal) ridge which may cross the forehead. Radiologic changes in the sella turcica in the form of unusual length and shallowness and an anterior "pocketing" (Figs. 2,*C* and 3,*C*) are striking and virtually pathognomonic. This type of sella is called "shoe-shaped" by Ullrich,[111] who found in other cases a shallow "shell-shaped" or a deeper "bowl-shaped" fossa.

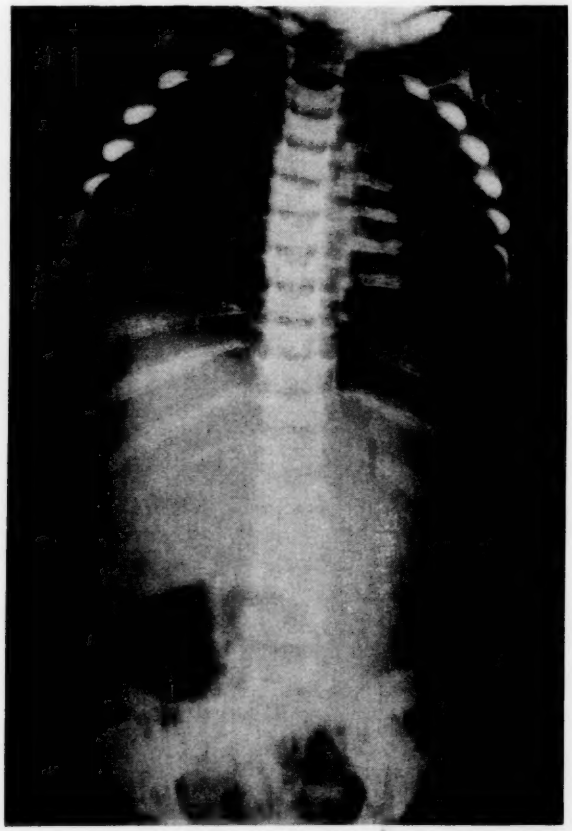
The lips are large and patulous. These, with the apathetic facies, the open mouth, and frequently enlarged tongue, may lead to a false diagnosis of cretinism. In general, the facial features are coarse and ugly. The teeth are usually small, stubby, widely spaced, and malformed. In many of the cases there is hypertrophy both of the bony alveolar ridges and of the overlying gums.[22] Chronic "rhinitis" with noisy mouth breathing is virtually universal in this group of

Fig. 1,*C*. *(For legend see opposite page.)*

patients. X-rays of the facial bones usually show marked deformities which are probably responsible for the nasal manifestations. On lateral view of the skull, it can often be seen that a mass of adenoid tissue in the nasopharynx is narrowing or obliterating the normal air shadow.

The neck is exceedingly short, and the thorax, on which the head appears to rest directly, is deformed. There is usually a flaring of the lower rib cage, prob-

ably due in part to the hepatosplenomegaly. Kyphosis with gibbus in the lower thoracic and upper lumbar area is likely to be present. Myelograms in one case revealed partial obstruction of the spinal canal at the level of the gibbus. Radiologic examination usually shows a wedge-shaped deformity of the body of the vertebrae with an anterior hooklike projection, so-called beaking of the vertebrae.



A.

Fig. 2.—Skeletal changes in the Hurler syndrome. *A*, The lower ribs are unusually broad and spatulous. Note the evidence of hepatosplenomegaly. *B*, The anterior pocketing of the sella, "shoe-shaped" sella, is highly characteristic. Furthermore, pronounced abnormality in the region of the paranasal sinuses is evident. *C*, The long bones of the arm are abnormally short and broad. The bones of the hand are strikingly abnormal in configuration. Again their shape is virtually pathognomonic of the Hurler syndrome.

The hands are usually broad with stubby fingers.[102] The fifth fingers are often bent radially, and, in general, there is likely to be at least partial flexion contracture of the fingers as well as of the larger joints. Limitation in extensibility of joints is usually striking.[56] This feature may be due both to deformity of the joint surfaces and to changes in the tendons and ligaments surrounding

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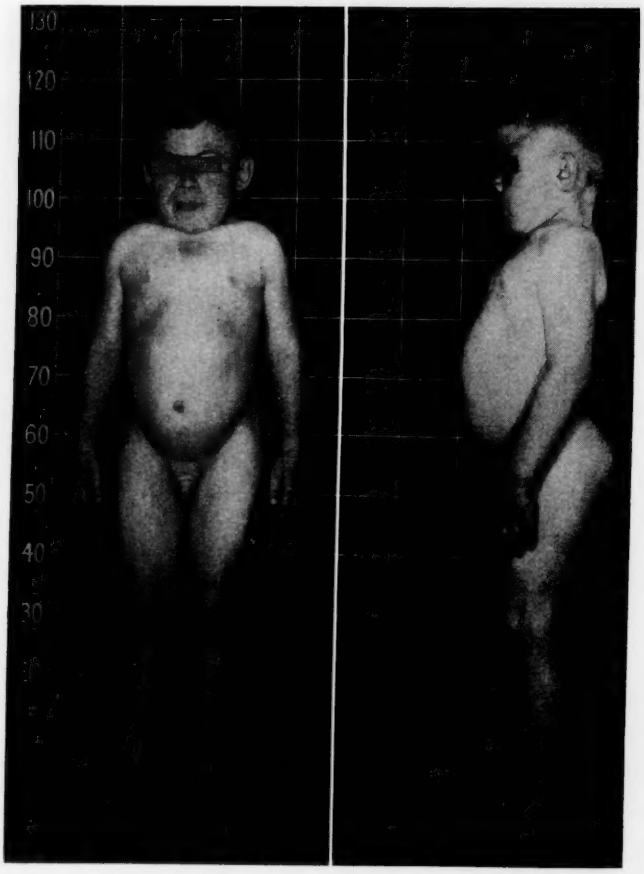
B.

C.

Fig. 2, *B* and *C*. *(For legend see opposite page.)*

the joints. As a result, the patients often find it necessary to walk on their toes, especially if they have been in bed a good deal. A deformity of the wrist may superficially suggest rickets. However, the stiff joints (along with many other features) help distinguish the Hurler syndrome[52]; the joints in rickets are more limber than normal. The limitation of motion of joints seems to extend to the thorax, which often is relatively fixed in position.[36]



A.

Fig. 3.—Typical case of the Hurler syndrome (I. S. 204375). *A*, At the age of 10 years.

The gibbus is often the first observed abnormality. When the infant begins to sit, he is likely to assume a posture like a cat's in sitting (Fig. 1,*B*), the "cat back deformity."

In addition to the radiologic changes already described in the skull and in the vertebral column, the bones of the extremities are abnormal in appearance. The phalangeal bones, for example, are short and misshapened (Fig. 2,*D*). The ribs are characteristically broad, sabre-shaped, or spatulate (Figs. 2,*A*, 2,*B*).

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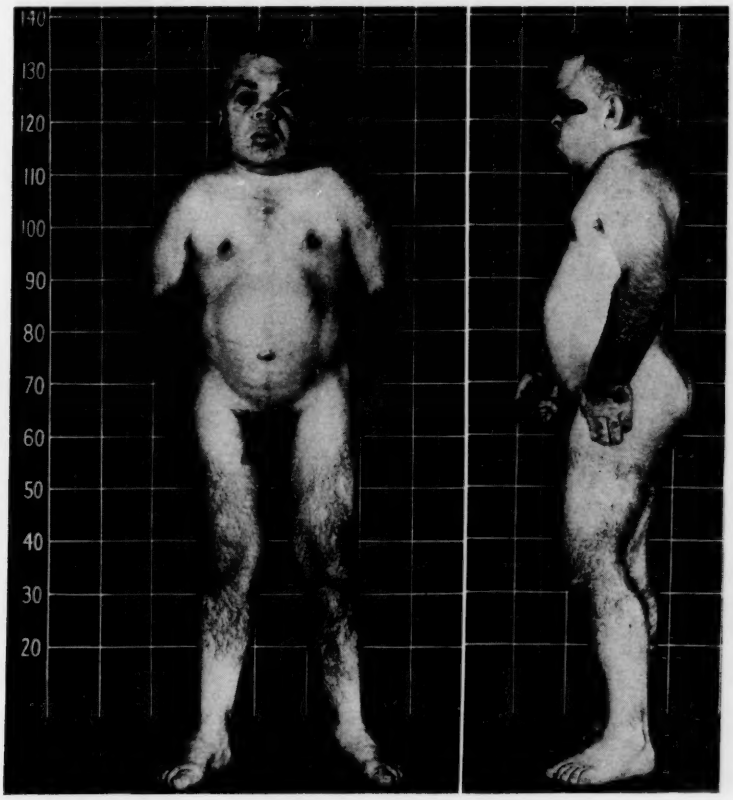
Genu valgum, coxa valga, pes planus, talipes equinovarus, and other deformities occur frequently. Hooper's patient[51] was operated upon for talipes equinovarus at the age of 17 years. Spina bifida occulta is occasionally present.

The abdomen is protuberant, due in part to hepatosplenemegaly, in part to the defect of the supporting tissues. Both liver and spleen may be so large that their lower borders dip into the pelvis. One patient developed pancytopenia and epistaxes, possibly on the basis of hypersplenism.[102] Lindsay[71] described an abnormal hippuric acid test in one patient, and, in another, prolonged elevation of galactose in the blood after intravenous injection. The number of patients



B. *C.*

Fig. 3.*B* and *C*.—Same patient at the age of 22 years.

tested was not stated. Although no systematic study has been made, the impression is given that surprisingly little functional impairment results from the marked gross and histologic involvement of the liver. One case of cirrhosis of the liver in a 37-year-old patient with quite typical Hurler's syndrome has been reported by Schwarz and Gagne.[98] Portal hypertension, massive ascites, hematemeses, melena, and death resulted. At necropsy the liver was found to weigh only 900 grams. In a 29-year-old patient[102] with fairly marked hepatospleno-

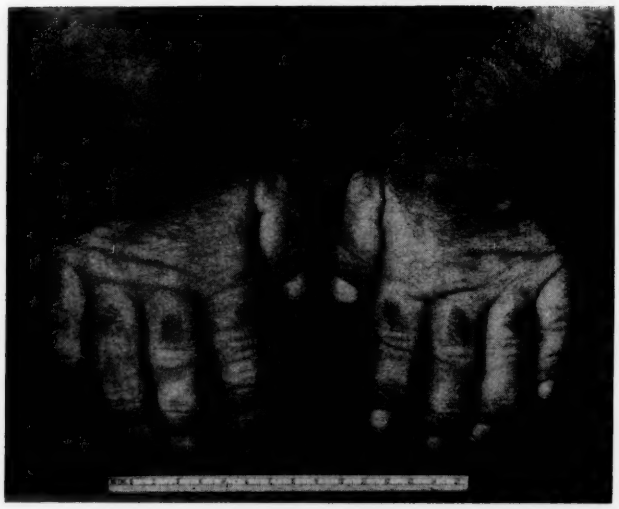


Fig. 3,*D*.—The hands.

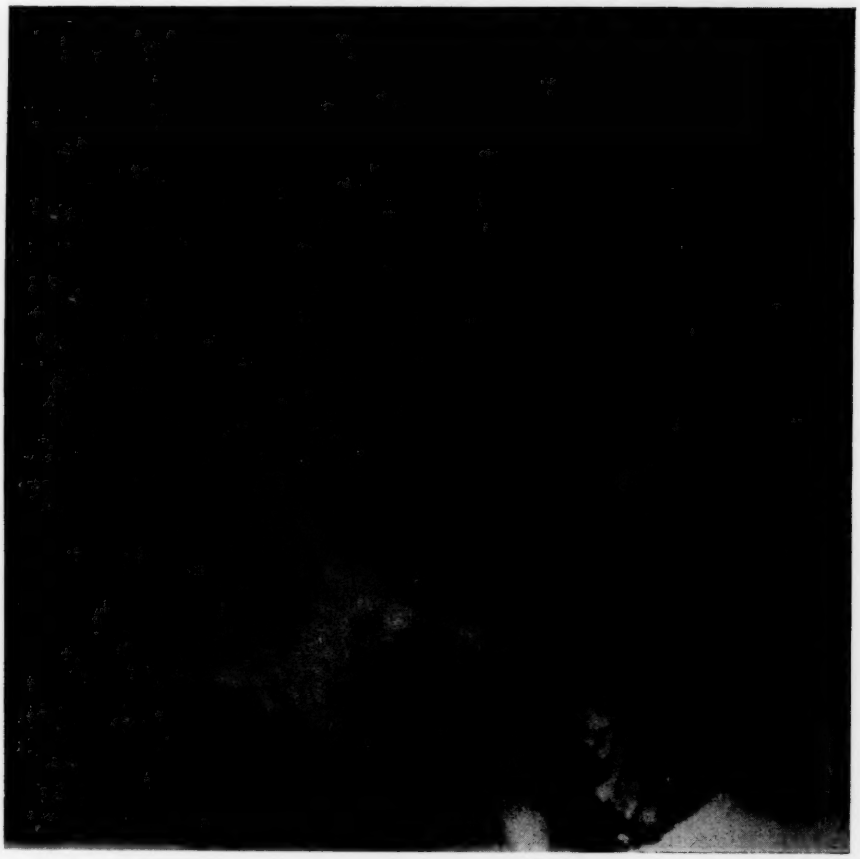


Fig. 3,*E*.—Lateral radiograph of skull. Characteristic anterior pocketing of the sella is present. There are obvious frontal and occipital areas of hyperostosis. The mastoid air-cells are underdeveloped and in general the mastoid is more dense than normal.

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Fig. 3,*F*.—Two uncles of the patient. Both probably had the Hurler syndrome.

Fig. 3,*G*.—The propositus (on left), aged 22 years, and his unaffected brother (on right), aged 8 years.

megaly, cephalin flocculation, thymol turbidity, total serum proteins, albumin-globulin ratio, prothrombin time and bromsulfalein excretion were all unequivocally normal. Many of the patients in my series have had these same tests with similarly normal findings. Moderate increases in serum cholesterol concentration do seem to occur more often than is normal and may be related to the liver disease.

Diastasis recti and umbilical hernia are almost invariable and inguinal hernia in frequent. Engel[37] described scrotal hernias the size of a child's head. Bilateral hydrocele is also seen.[47]

"Funnel chest" was present in one of Hurler's cases[63] and one of mine.

Changes in the skin[69] in the form of grooving and either ridged[19] or nodular[1] thickening, expecially over the upper arms and thorax, have been described. In two of the reports[1,19] the changes were strikingly similar, especially as to location —"symmetrically distributed in an area of about 6 by 10 cm., extending from the angle of the scapula towards the axillary line." In most of the cases the entire surface of the body, both trunk and extremities, is covered by fine, lanugo-like fuzz. In older patients, too, hairiness is quite striking, especially over the arms and hands (Fig. 3).

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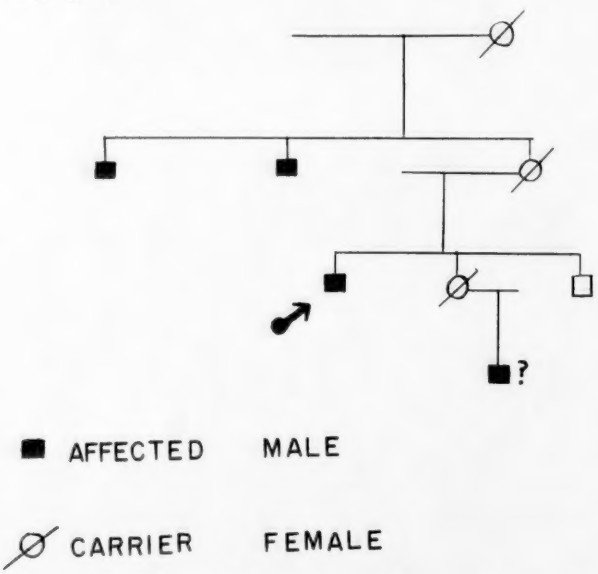

Fig. 3,*H*.—Pedigree. The propositus is indicated by the arrow. The probable occurrence in four males in three generations is consistent with, and at least mildly indicative of, inheritance of the trait as a sex-linked recessive. The females marked with the line, in fact all the females included in the pedigree, are presumed to be genetic carriers for this trait.

This patient, 22 years old in Fig. 3,*B* and on most recent study, has dysostosis multiplex, deafness, "chronic rhinitis," exertional dyspnea, hepatomegaly, restricted joint mobility, hydrocele, and hernia, but no splenomegaly or corneal opacification. Mentality is retarded. The patient graduated from high school because of courtesy promotions. He reads voluminously, especially Ellery Queen novels! No inclusions could be demonstrated in the white cells. The testes are small and soft. However, the patient shaves daily and erections and nocturnal emissions occur. Vision was 20/100 in the right eye, 20/30 in the left. A startling finding was bilateral papilledema, probably long-standing, with "bone corpuscle" pigmentary degeneration of both fundi, especially the right. A peculiar feature has been the subjective response to thyroid. Two maternal uncles (Fig. 3,*E*) had the Hurler syndrome with characteristic skeletal features, deafness, and symptoms of cardiac incompetence. They died at the ages of 12 and 17 years, one having been found dead in bed. The patient's parents are normal and he has two normal siblings. An 8-month-old nephew of the patient may have the disease: I have not had an opportunity to examine the child but the descriptions are suggestive.

No consistent endocrine abnormality is clinically detectable, in spite of the histologic evidence of cellular deposits in most glands of internal secretion. Thyroid enlargement without dysfunction has been described and is probably related to the histologic infiltration referred to. Hypoglycemia from hepatic involvement is thought to be a risk but has not actually been demonstrated to my knowledge.

Inclusions (Adler bodies) in the polymorphonuclear leukocytes are sometimes found.[90] These are described as being larger than the ordinary granules and tending to take a dark lilac color when stained by the Giemsa-Wright technique. In a number of the cases seen in this hospital, Dr. C. L. Conley has looked for inclusions without success. Although others[9,31] have confirmed Reilly's[90] original observation, the occurrence of leukocytic granules may not be as frequent as often thought.[113] The inclusions have histochemical characteristics suggesting identity with the material which balloons cells of other parts of the body.[72] (Apparently, inclusions may also occur in the leukocytes in glycogen storage disease.[12,116])

Clouding of the cornea has been described in about 70 per cent of reported cases. The cornea usually has merely a steamy appearance in earlier stages. On inspection this feature is most apparent if light is shined on the cornea from the side.

Ullrich[111] found, up to 1943, fifty-one cases with corneal involvement, eighteen without. Although the number of cases with evidences of corneal involvement is increased by slit-lamp examination, there are certainly some with none. Slit-lamp reveals that the opacities are located in the medial and deeper layers of the cornea. The epithelium and endothelium are spared. Other ocular abnormalities such as buphthalmos[26] and megalocornea[5,34,63,80] have been described. There may be a retinal element in visual impairment since histopathologic changes in the retina have been described.[72] The occurrence of papilledema in these patients (see Fig. 3) has suggested hydrocephalus, or at least increased intracranial pressure. Optic atrophy was described in two siblings by Davis and Currier.[23]

Mental retardation may be only mild in some cases. Hydrocephalus may occur in severely affected infants.[2,71] Some cases may show simple dilatation of the ventricles secondary to cortical atrophy.[111] The mental deterioration is likely to be progressive, resembling juvenile amaurotic idiocy in this respect.[63] There may be accompanying neurologic signs such as motor paralysis, increase in muscular tone, and the Babinski sign.

One would presume that the deafness is in the main secondary to the bone disease as in osteogenesis imperfecta. In a 24-year-old patient studied by Dr. William G. Hardy of the Johns Hopkins Hearing and Speech Clinic, the deafness was found to be of perceptive type. In a 16-month-old child it was of the conductive type, and in a 3-year-old patient hearing was unimpaired. Because of the deformity of the nasopharynx, these patients probably have more than the average susceptibility to middle-ear infection. Furthermore, the ossicles have shown deformity with limitation of joint motion as in other joints and bones.[120] Therefore, a conductive element in the deafness of some patients is to be expected.

Nasal congestion, noisy mouth breathing, and frequent upper respiratory infections occur in essentially all patients with the Hurler syndrome. The malformation of the facial and nasal bones is probably in large part responsible.

A. *B.*

Fig. 4.*A* and *B*.—Three siblings, aged 8, 6, and 12 years, respectively, left to right. The brother in the middle, aged 6, is normal. The brother and sister on the sides have been thought to have Morquio's syndrome, but review of the total clinical picture suggests that Hurler's syndrome may be present. They are markedly dwarfed. There is limitation of motion of many of their joints. This is visible in the pictures. Contractures of the fingers began to develop at the age of about 18 months. The immobility of joints is in part the result of distortion and dislocation of the epiphysis but seems in part the result of changes in connective tissues about the joints. There is no gibbus, but by x-ray beaking of lumbar vertebrae is demonstrated (Fig. 4.*E*). Mentality is roughly normal and both children are lively and energetic. Teeth are wide-set, piglike, susceptible to caries. Both children are already somewhat deaf. The 8-year-old affected brother has hypospadias; sexually the affected sister appears to be developing normally although catamenia has not yet occurred. The affected boy had a strangulated left inguinal hernia at the age of 1 year, and a strangulated right inguinal hernia at the age of 2 years. Umbilical hernia has been present for several years. Both children have heart murmurs. The boy's is apical, the girl's basilar. In both, the murmur has a groaning quality and is believed to be innocent. The parents are normal and there are two other normal children. In the affected girl the liver and spleen are not thought to be enlarged. In the boy the liver was 4 to 6 cm. below the costal margin and the spleen was 4 to 5 cm. down (at the age of 3 years neither had been considered enlarged). In both, the corneas are clear. ECG and EEG are normal. It is not difficult to understand why the idea has arisen that the Morquio syndrome may occur in one member of a sibship and the Hurler syndrome in another.[8]

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D.

C.

Fig. 4,*C.*—The fingers are being held in maximum extension possible. Note the contractures.

Fig. 4,*D.*—X-ray of the hands revealed moderate coarsening of the bones but not as marked changes or the specific change in shape seen in Fig. 2,*D*. The contractures seem to be the result of changes in the soft tissues.

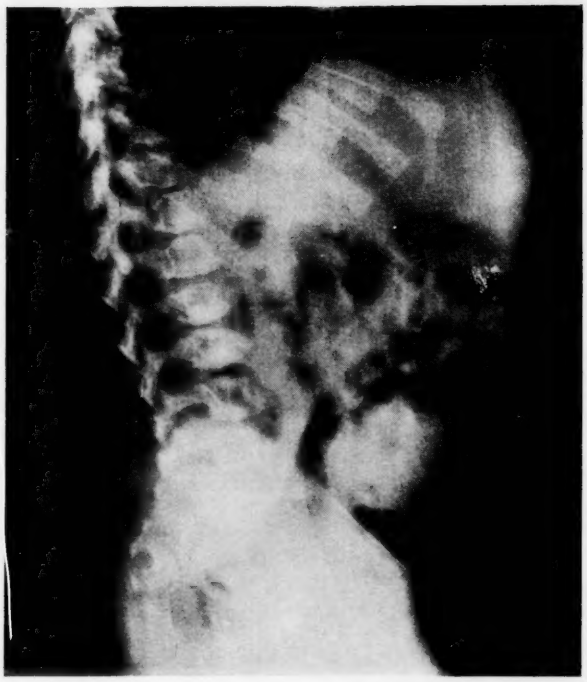

Fig. 4,*E*.—Lateral view of the spine in affected girl. Note the same sabrelike ribs and beaking of the lower margin of the vertebrae as in Fig. 2,*B*.

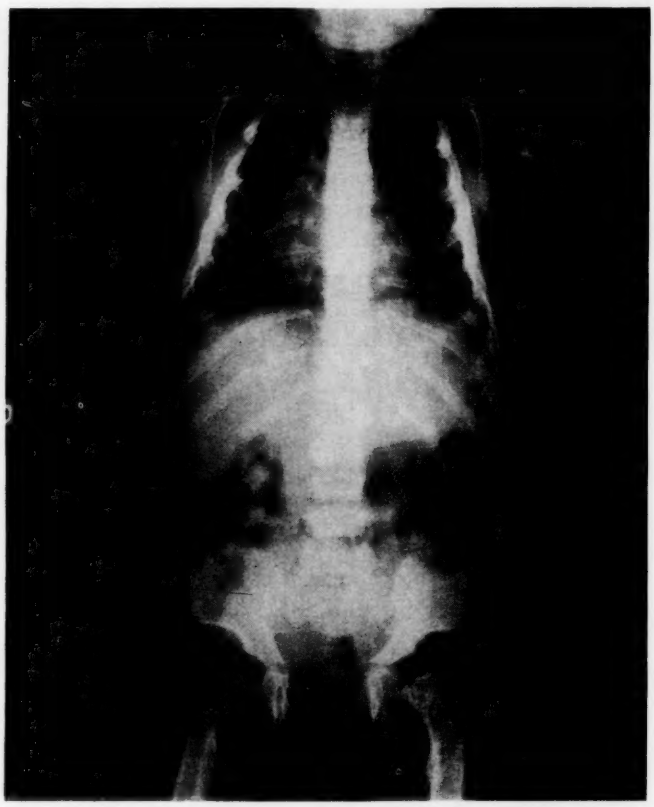

Fig. 4,*F*.—Frontal view of skeletal system in affected girl. Note the advanced changes in the epiphyses of each femur and humerus.

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Ellis, Sheldon, and Capon[34] commented on this feature. Most other writers have also emphasized it and considered malformation of the nasopharynx to be its basis.

In Hunter's historic report[55] he remarked on the occurrence in one of his patients of cardiomegaly and both systolic and diastolic murmurs. Murmurs were described also by Meyer and Okner,[80] Engel,[37] and others. Ashby, Stewart, and Watkins[2] described "congenital heart disease" as the cause of death at 9 years of

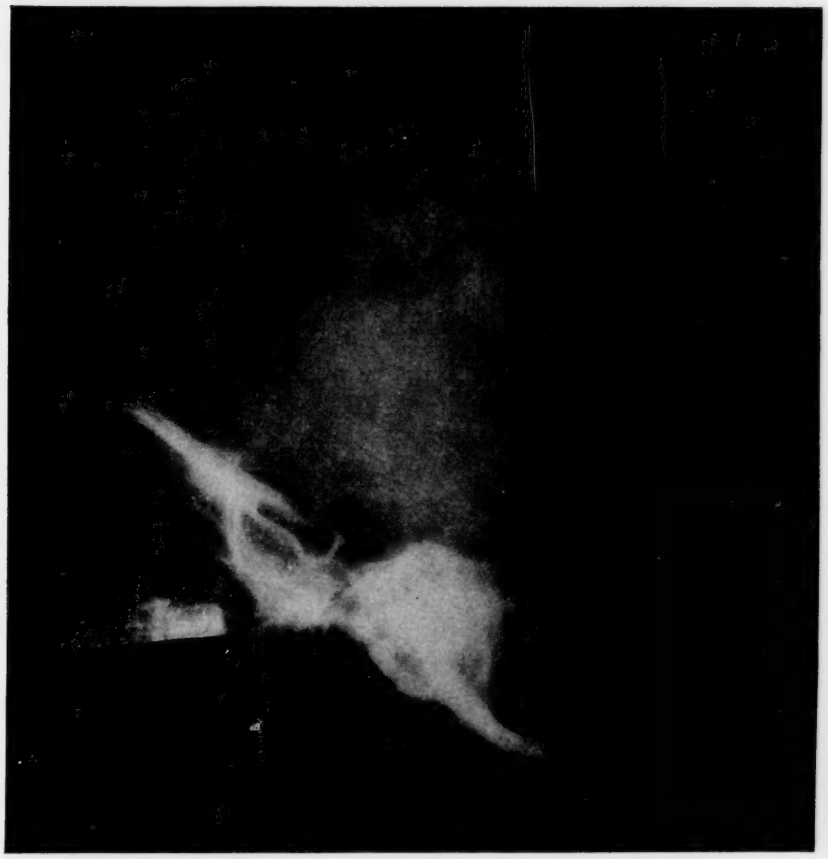

Fig. 4,*G*.—Note marked anterior pocketing of the sella. Compare with Fig. 3,*C*. Clinically there is a ridge running sagittally over the skull (scaphocephaly).

age in one child and in a 19-year-old patient who died suddenly. Mouth breathing and dyspnea from thoracic deformity and restriction of expansion[36] (which may be very striking), abnormality of the bronchial cartilages, and, finally, frequent attacks of bronchitis make it difficult to dissect out that part of the dyspnea which is on a cardiac basis. The best specific descriptions of the cardiovascular aspects of the Hurler syndrome are those of Lindsay[71] and Emanuel.[36] Emanuel described in two brothers cardiac signs he interpreted as being those of pulmonary hypertension. In one, cardiac catheterization was performed with demonstration

of a much elevated pulmonary artery pressure (88/50 mm. Hg). The peripheral arteries of the arms were described as thickened in a 6½-year-old child[72] and there was hypertension (132/100 mm. Hg).

What was interpreted as angina pectoris occurred[22] as early as 4¾ years of age in a child who died at the age of 7 years. The extensive occlusive disease of the coronary arteries discovered at autopsy in this child would suggest that this is the basis of sudden death in many of these patients.

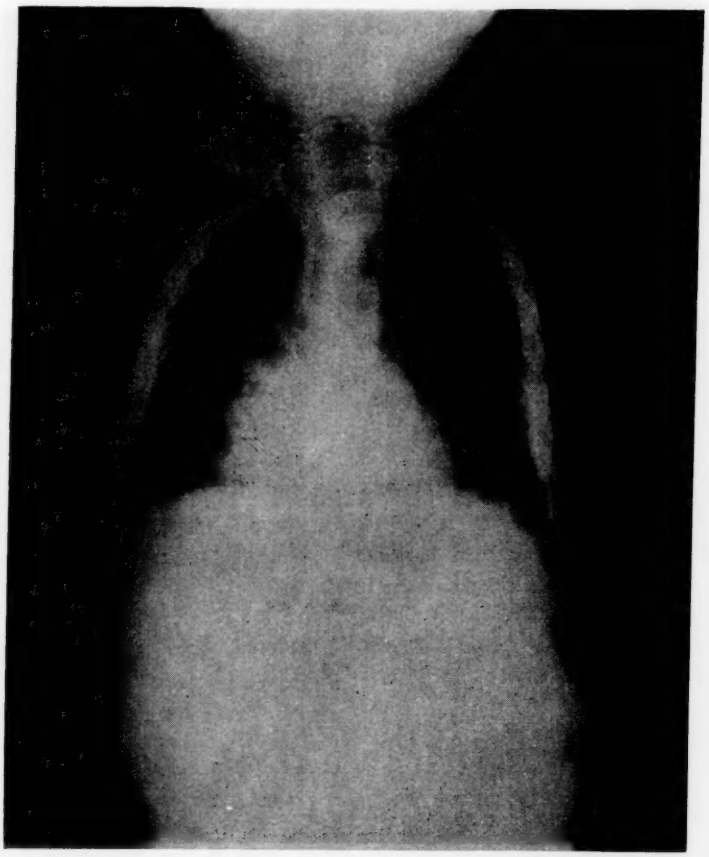

Fig. 5.—Chest x-ray in G. V. D., Jr. (B2188), aged 4½ years. This patient has the Hurler syndrome in entirely typical form. He reached a peak of intellectual development at about 2 years and has deteriorated since then. Gibbus was noted at 1 year. Thick skin, lanugo, "shoe-shaped" sella, and ground-glass corneas are present. Hydrocele and right inguinal hernia were treated surgically at the age of 1½ years.

The central infiltration of the lung fields was present in an unchanged form for at least six months. Tuberculin skin tests are negative. The changes are believed to be the result of chronic bronchitis. However, interstitial pulmonary infiltration as part of the disease and analogous to the infiltrations elsewhere cannot be excluded.

Lindsay[71] stated that systolic murmurs along the left sternal border were so striking in these patients that four of sixteen were suspected of having an

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interventricular septal defect. There was a similar clinical experience in the group of cases at this hospital. The experience with other heritable disorders of connective tissue, specifically the Marfan and Ehlers-Danlos syndromes, in which cardiac malformations of the conventional type occur with predictably increased frequency, suggests that the same might occur in the Hurler syndrome. Pathologic studies have not corroborated this suspicion (see below). Although some cardiovascular abnormality was present in the great majority of patients who have died, all the changes have been of a specific type, as described later.

Death from "heart failure" (either congestive or coronary artery in type) often occurs before the age of 20 years. Of the patients described by Smith, Hempelmann, Moore, and Barr,[102] one died at the age of 28 years and another was "reasonably well" at 29 years of age. Hooper[51] described a 37-year-old patient who was still living. In two of his other patients, death occurred at 20 and 30 years of age, respectively. The two oldest patients in my series are 22 and 25 years old, respectively (see Fig. 3 for one of these). Beebe and Formel[4] described nine well-documented cases of the Hurler syndrome in one family. Five had died at an age in excess of 40 years. There were four survivors aged 45, 43, 17, and 14 years, respectively.

PATHOLOGIC CHANGES[38]

At least thirty autopsies have been reported in detail: eighteen individual reports,[2,4,30,36,42,49,66,67,68,76,81,96,98,102,105,106,110,111,113,117] two by Jervis,[63] and eight by Lindsay, Reilly, Gotham, and Skahen.[72] Jackson[58] and others have reported on biopsies of the liver.

Among other sites, abnormalities have been identified in cartilage, fasciae, tendons, periosteum, blood vessels, heart valves, meninges, and cornea. All of these may contain cells which are thought to be of the fibroblast line and which are distended with large amounts of deposited material. These are appropriately called "clear cells" by Millman and Whittick,[81] but perhaps it would be preferable to use the more specific designation "gargoyle cells."[109] In addition, collagen in many of these areas has been said to look abnormal in a poorly defined way. Collagen fibers are described by some (e.g., ref. 71) as swollen, homogeneous, and lacking in their normal fibrillary characteristics. Material, presumably identical to that in the fibroblasts, balloons the nerve cells of both the central nervous system and the peripheral ganglia, the nerve cells in the nuclear layer of the retina,[72] the Kupffer cells of the liver, the parenchymal cells of the liver, the reticulum cells of the spleen and lymph nodes, and the epithelial cells of several endocrine organs such as the pituitary[68] and testis. Mental retardation and hepatosplenomegaly are explained by these deposits.

Enlargement and vacuolization of the chondrocytes and osteocytes, as well as of the periosteal cells, are described and probably are intimately related to the skeletal malformation.

In the heart, in persons dying after a few years of life, the aortic and mitral valves almost invariably have shown some degree of nodular thickening.[36,72] Functionally both stenosis and regurgitation can result. In the case of Smith and co-workers[102] the histologic picture in the heart valves was dominated by the

presence of "gargoyle cells." These have also been seen in the coronary arteries.[72,76] Grossly[36] even in young individuals the coronary arteries may "stand out like white cords." Virtually complete occlusion may result from the extensive intimal deposits.[22,27] The aorta[76] and pulmonary artery[36] may show extensive intimal deposits, presumably of the same material as forms the vacuoles of the cells of various organs. The myocardial cells may show marked ballooning by vacuoles (see photomicrograph, ref. 6). Patchy thickening of the endocardium and epicardium is described.[36,72,106] Of the peripheral arteries, changes have been described in those of the brain, spleen, pancreas, and kidney as well as in the mesenteric, carotid, radial, and anterior tibial arteries.

Emanuel[36] was able to find 32 autopsy reports in which specific description of the heart was provided in 26. Of these 22 had cardiovascular abnormalities (85 per cent). In 15 patients the mitral valve was deformed, in 9 the aortic, in 7 the tricuspid, and in 2 the pulmonary. In three (including Emanuel's case) all four valves, the epicardium, the endocardium, the coronary arteries, and the aorta and pulmonary artery were involved.[72,106]

It is of note that the order of incidence of involvement of the heart valve—mitral, aortic, tricuspid, pulmonary—is precisely as in rheumatic fever. In both situations there are probably operating at least two prominent factors. The metabolic aberration (in one case acquired, in the other inherited) and the hemodynamic stresses. The peak pressures sustained by the four valves in the position of closure are in the same sequence as the incidence of valve involvement: mitral, 120* mm. Hg; aortic, 80 mm. Hg; tricuspid, 25 mm. Hg; pulmonary, 12 mm. Hg.

A conventional type of congenital malformation of the heart has been thought clinically to be present in three of the patients seen at this hospital. Seemingly, however, no such malformation has been revealed by any of the pathologic studies.

Abnormality of the tracheobronchial cartilages together with that of the upper airways may be responsible for the susceptibility to respiratory infections in these patients. Bronchopneumonia is a frequent cause of death.[63]

Cole and associates[19] illustrate a histologic section of skin which was interpreted as showing "marked fragmentation of collagen fibers and mucinous degeneration."

Vacuolated cells have been described in Bowman's membrane by Berliner[5] and others. Lindsay and co-workers[72] described highly metachromatic granules in the cornea.

Multiple abnormalities in the middle and inner ear have been discovered in one twice-reported case.[102,120]

Extensive changes in the leptomeninges were described by Magee.[76] The coincidence of subdural hematoma in his case makes these changes difficult to interpret. Millman and Whittick[81] found thickening of the leptomeninges over the cerebral hemispheres and "clear cells" histologically. In Njås[85] case 2, there was hydrocephalus with "thickened and milky leptomeninges." The hydrocephalus may be the result of interference with drainage produced by the deposits characteristic of the disease.

*All values are approximations.

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Some have reported that the intracellular deposits do take the conventional fat stains.[6,46,110] Most have found that the vacuoles do not stain as fat or stain atypically.[102] Analyses of hepatic and splenic tissue for fat reveal no increase.[49,105,109] The material does stain with periodic acid-Schiff's reagent (PAS), may stain with Best's carmine and displays striking metachromasia.[113] Formalin or alcohol-fixed material dissolves the vacuolar material. Dioxane-dinitrophenol fixative has been useful[72] in preserving the deposited material.

Histochemical studies led Lindsay and his collaborators[72] to suspect that the storage material is glycoprotein. Brante[11] isolated a material, polysaccharide in nature, having 0.9 per cent sulfur, 27 per cent hexosamine, and 26 per cent glucuronic acid, containing no fatty acids by hydrolysis, and representing 10 per cent of the dry weight of the liver. Uzman[113] has recently described two storage materials isolated from the liver and spleen of these patients: (1) a complex polysaccharide containing glucose, galactose, hexosamines, and sulfate, soluble in water and formaldehyde but insoluble in other organic solvents, and staining metachromatically with toluidine blue; (2) a glycolipid soluble in water and ethanol but not in other organic solvents, and containing fatty acids, sphingosine, neuraminic acid, hexuronic acid, hexosamines, glucose, and galactose. These Uzman refers to as Fractions P and S, respectively.

Dawson[27] thought that the deposits in the brain consisted of phospholipid although those elsewhere seemed to be mucopolysaccharide. Uzman[113] did not study brain.

THE FUNDAMENTAL DEFECT

Straus, Merliss, and Reiser[105] thought that this might be a dystrophy of collagen, and Cole and his co-workers[19] also subscribed to this view. These authors based their view mainly on the lack of good evidence of this being a lipid-storage disease and the fact that contractures of joints and hernia occur, as well as skin changes which Cole interpreted as involving primarily collagen.

On the other hand, Ellis and colleagues[34] considered gargoylism (as they called it) a disorder of lipid metabolism. Washington[117] in his term "lipochondrodystrophy" implied the same theory.

de Lange and co-workers[29] and Strauss[106] thought the storage material might be a glycogen. Lindsay and co-workers[72] suggested that the stored material might be a polysaccharide (such as glycogen) or glycoprotein. Brante[11] studied three cases clinically and histologically and came to the conclusion that the Hurler syndrome is a "congenital enzyme disturbance as regards the metabolism of the mucopolysaccharide or of some of its components, or as regards the binding of the mucopolysaccharide to protein, etc." The qualitatively and/or quantitatively abnormal mucopolysaccharide accumulates at various sites, according to the last view.

Uzman[113] appears to take a slightly different view, which, however, to the nonchemist is not too evidently distinct. He holds that the genetic defect is one concerning the metabolism (i.e., synthesis) of "structural polysaccharides" which are normally important building blocks of connective tissue elements.[41]

The manner in which abnormal deposits occur in the intima and elsewhere is reminiscent of the handling in rabbits of methylcellulose and pectin,[53,54] both of which are macromolecular carbohydrates. Hueper[54] observed ballooning of cells in the liver, spleen, kidney, arterial intima, bone marrow, and anterior pituitary when pectin was administered intravenously in rabbits and dogs. However, "no lesion was found in the cerebral parenchyma, the vascular system of the brain or the choroid plexus."

The clinicopathologic differences between the Hurler syndrome, on the one hand, and the syndromes of Gaucher and of Niemann and Pick, on the other, are suggestive evidence that the storage material in the Hurler syndrome is not lipoid. In neither Gaucher's disease nor Niemann-Pick's disease are the parenchymal cells of epithelial organs involved. (Thannhauser[109] refers to Gaucher's disease as "reticular and histiocytic cerebrosidosis" and to Niemann-Pick's disease as "reticular and histiocytic sphingomyelinosis.") The bone lesions of Gaucher's disease, such as the Erlenmeyer flask deformity of the long bones, result from the involvement of the marrow and not from the implication of fundamental skeletal building blocks as in the Hurler syndrome.

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The duality of the storage material, as demonstrated by Uzman,[113] requires explanation. He proposes that the accumulation of one may be a direct result of the genetic defect and the other an ancillary effect resulting from interference with normal cellular function as a result of the deposition of the first. Uzman[113] considers his Fraction P to be more directly concerned with the basic defect of this disease.

The fact that the skeletal deformity is invariable, whereas the mental retardation, corneal clouding, and hepatosplenomegaly are inconstant and progressive is consonant with the idea that the skeleton is affected in a primary manner by the connective tissue defect, and that the other manifestations are, in the main, secondary "storage" phenomena, a thesaurosis.

Meyer[78,79] states that chondroitin sulfate A, the main mucopolysaccharide of hyaline cartilage, has been identified in only one other tissue—cornea. There is a possibility, then, that the corneal involvement might be a primary feature of the syndrome, as we are presuming the dysostosis to be, and not a secondary feature due to deposit of an anomalous polysaccharide.

It is probable that the basic defect in the two genotypes of the Hurler syndrome (*v. seq.*) is slightly different. The phenotypic differences would suggest this to be the case.

INCIDENCE AND INHERITANCE

This disorder is more common in males than females. Few, if any, cases have been described in Negroes. The syndrome has been reported in Chinese.[37]

More often than not, the Hurler syndrome displays features of inheritance consistent with a recessive autosomal trait.[44] Parental consanguinity[8,44] is frequent, and affection of multiple sibs without the occurrence of affected individuals in the preceding generation ("familial" characteristics) is often the case. In the series of patients seen in this hospital, there is one instance of the disease in two sisters with normal parents and three normal siblings. There are no

well-documented descriptions of skeletal deformities in close relatives of patients with full-blown cases to suggest that partial expression of the trait in the heterozygous state may occur. Concordance in identical twin sisters has been described.[86] Craig[22] described the disorder in a twin brother and sister.

In 1952, Jervis[63] reviewed the information on 103 families described in the literature. When the ratio of affected to unaffected sibs was corrected by the method of Bernstein and that of Lenz, statistically significant agreement with the expected 1:3 ratio was obtained. Cousin marriages are *known* to have occurred in 11 of the 103 families and probably actually occurred in more. Using Hogben's formula, Jervis calculated that a 10 per cent consanguinity rate would correspond to a gene frequency of 1 in 40,000.

As far as is known, none of these patients has procreated. Some of the patients with milder affection may be capable of reproduction. Because of the statistical unlikelihood of mating with a carrier for the disease trait, unless the mate is a relative, the offspring of an affected person can be expected to be normal but will of necessity be a carrier for the trait if the theory of the recessive inheritance of the Hurler syndrome is correct. Actually the individuals most capable of reproducing are all males who may have the sex-linked variety of the disease (*v. seq.*). This means that none of their sons would be affected but half the daughters would be carriers.

A seemingly sex-linked form is described in at least five reports,[4,74,81,85,120] and, of course, there are many other instances in which this theory of inheritance is consonant with the known facts.[19,30,36,55,64,74,75] In these cases the inheritance follows the pattern of a recessive x-chromosome factor, such as hemophilia. Njå[85] suggested that cases without corneal opacity are most likely to show this mode of inheritance.

In the fascinating report by Beebe and Formel,[4] nine cases were described occurring in four generations of a family of Dutch extraction which has resided in the Catskill Mountains for about 250 years. Of 19 males, 9 were affected. Of 16 female siblings of affected males, none was affected. All 9 affected males were related through their mothers, who were presumably carriers. Furthermore, they were all descended from a common female ancestor who was almost certainly likewise a carrier or perhaps started the disease (by mutation), just as Queen Victoria probably initiated hemophilia[103] in the royal houses of Europe. Five other females could be identified as carriers by reason of affected brothers and sons. Six females had borne only normal children.

The family described by Beebe and Formel[4] may corroborate Njå's[85] impression that the sex-linked disease is a different entity clinically as well as genotypically. The sex-linked form of the disease may pass unrecognized until the age of 4 to 8 years. Mentation is usually less severely affected. The patients live longer. Finally, there is no corneal involvement. Fig. 3 presents the case of a patient with Hurler's syndrome, probably of the sex-linked variety.

After reviewing the literature on the Hurler syndrome in the light of the thought-provoking papers of Beebe and Formel[4] and of others, I have become convinced that there are at least two genotypes of the Hurler syndrome. Futhermore, it seems that there may be slight phenotypic differences corresponding to the genotypic differences, as outlined in Table I.

TABLE I

	AUTOSOMAL RECESSIVE	SEX-LINKED RECESSIVE
Corneal clouding	4+	±
Retardation of intellect	2+ to 4+	± to 2+
Gibbus	2+ to 4+	±
Age of death	Usually under 20 years	Often over 40 years
Reported cases	The majority, e.g., refs. 22, 47, 48, 63, 86, 93	Quite definite examples: refs. 4, 74, 81, 85, 120; likely examples: refs. 19, 30, 36, 55, 64, 74, 75
Personal cases	Probably fourteen cases	Probably two pedigrees (see Fig. 3 for one)

It would seem significant that most of the patients known to have survived beyond the age of 20 years (see above) were male. In Jervis' survey[63] there were 145 cases in which the sex was stated; of these, 93 (64 per cent) were male. Of 112 sibships, 65 could, by reason of the fact that all affected individuals were male, represent the hypothesized sex-linked variety of the disease. There were 27 sibships with more than one affected individual; of these, twelve had only males affected, only four had only females affected, and in eleven both males and females were affected. The average age of the affected individuals in the sibships with more than one affected individual, all males, was 6.65 years. The comparable value for the sibships containing both male and female affected individuals was 10.02 years. Although this appears to contradict the rough impression that the patients with the sex-linked variety of the Hurler syndrome are older when they come to medical attention and when they die, it must be remembered that these collected sibships may contain some in which the trait was inherited as an autosomal recessive; these may weigh down the average.

Again following Jervis'[63] survey the state of the cornea was analyzed in (1) the isolated female cases plus the sibships with affected persons of mixed sex, and in (2) the isolated male cases plus the sibships with affected persons all male. In the case of multiple affected sibs all affected persons in that sibship were counted as having cloudy cornea if one was said to show it. In sibships of the first type, the cornea was described in 69 individuals, of whom 51 (74 per cent) had corneal clouding. In category 2, the cornea was described in 70 individuals, of whom 39 (55.6 per cent) had corneal clouding.

Parents have been invariably unaffected. The difficulties in distinguishing autosomal from sex-linked recessive inheritance are well illustrated.

One may conclude that there are sex-linked and autosomal recessive forms of this disease, the latter being several times more common than the former.* If it were not for the confusion it would create, one might, with historic justification, refer to the disorder inherited as an autosomal recessive as the Hurler syndrome, and to that inherited as a sex-linked recessive as the Hunter syndrome (see Historical Note).

*In one report,[18] dominant inheritance is claimed, however.

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DIFFERENTIAL DIAGNOSIS

At least superficially, there are many resemblances between the *Hurler syndrome* and the *Brailsford-Morquio syndrome.*[10,82] In fact, it has been claimed that the two syndromes occurred in different members of the same family.[8] Fig. 4 describes an experience which makes me skeptical of such reports. de Rudder[92] has suggested that the Hurler syndrome is merely a combination (through gene linkage) of Morquio's dysostosis with what he calls a "phosphatide diathesis." Actually, as was discussed in Section I, gene linkage probably plays no role in hereditary syndromes. Cases are pointed to in which it appeared that only the "phosphatide diathesis" existed, e.g., by Grebe.[43]

Brailsford-Morquio chondro-osteodystrophy was independently described about 1929 by the two observers[10,82] whose names identify the syndrome. Morquio's name is more commonly associated with the disease than is Brailsford's. The disorder[3,4,9,13,21,23,32,33,35,77,84,89,100,107,118,123] is usually first detected at the age of less than 1 year, when a thoracolumbar kyphos is noted. The disease is characterized by kyphosis and failure of the trunk to grow in length whereas the extremities grow in a more nearly normal manner. The patients are dwarfed. Radiologically the vertebrae display wedge deformities or, more commonly, platyspondyly, i.e., flat vertebrae. In the extremities there may be palpable enlargement of the epiphyses which may superficially suggest rickets, a frequent misdiagnosis. The skull, mentality, corneas, liver, and spleen are usually normal. These normal features and the relatively mininal affection of the limbs permit differentiation from the Hurler syndrome. In some cases the joints are hypermobile (as described by Morquio), but in others they exhibit limitation of motion. The evidence of an hereditary basis is clear-cut although the precise mode of inheritance is seemingly variable. The variable inheritance may indicate that a phenotypic similarity leads to classification together of several disorders which are fundamentally distinct. In Jacobsen's very interesting family[60] the disorder was traced through five generations with twenty affected individuals, all male. The genetic behavior was thought to be that of a sex-linked recessive like hemophilia. (Interestingly, two female carriers of the trait had "marked arthritic processes in the hips and ankles.") In other instances inheritance as an autosomal dominant or an autosomal recessive has been hypothesized.

The difficulties in differentiating the Morquio and the Hurler syndromes are illustrated by the siblings shown in Fig. 4. Although the disease in this brother and sister was labeled Morquio's syndrome earlier, hernia, contractures, deafness, "shoe-shaped" sella turcica, sagittal ridge of the skull (scaphocephaly), the marked affection of the extremities, and in one hepatosplenomegaly suggest the Hurler syndrome. It is true that neither of these patients has the marked deformity of the facial bones with noisy breathing as in the case of the Hurler syndrome. Furthermore, corneal clouding and mental impairment are not present. Here the syndrome seems to have been inherited as an autosomal recessive.

The difficulties of differentiating Morquio's syndrome and Hurler's syndrome are also well illustrated by the report of Davis and Currier.[26] Although entitled

"Morquio's Disease; Report of Two Cases," the patients were described as having striking hepatosplenomegaly, "shoe-shaped" sella, claw hands, and contractures in other joints. Most subsequent authors have accepted these as cases of the Hurler syndrome. Ruggles[93] applied the label of Morquio's syndrome to the disorder present in three members of a sibship totaling seven. However, the presence of deafness, mental defect, and cloudy cornea makes the Hurler syndrome likely.

As in the "collagen-vascular" group of acquired connective tissue diseases, there appears to be in the group of chondrodystrophies a clinical spectrum such that one entity blends smoothly into the next and it becomes impossible to say with certainty where one entity leaves off and the next begins. With the "collagen-vascular" group, increasing familiarity has sharpened up the boundaries of the individual entities. It is to be hoped that the nosography of chondrodystrophies will be advanced to a like degree. It is my impression that there are several entirely distinct dysostoses such as Morquio's and Hurler's, and that it is only our ignorance which results in confusion of one with another. Quite the opposite view, namely, that Morquio's syndrome and Hurler's syndrome are clinical variants of what is fundamentally the same disorder, is expressed by Eichenberger.[31]

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Reduced joint mobility such as is seen in the Hurler syndrome is a characteristic of *arthrogryposis multiplex congenita*. In fact, in an extensive recent survey James[60] prefers to use the designation of "multiple congenital articular rigidities" as suggested by Nové-Josserand, rather than the more generally used term proposed by Stern.[104] Subluxation, especially of the hips, may occur in this condition of tight joints just as it does with the loose-jointedness of the Ehlers-Danlos syndrome. Rigidity of the temporomandibular joint may create a feeding problem in severely affected infants. The patella may be rudimentary or absent. The subcutaneous tissues are likely to feel thick, doughy, and gelatinous. In general the subcutaneous tissues may be deficient, or may be excessive so that the limbs have the appearance of stuffed sausages. The peripheral circulation tends to be poor and the limbs cold. Inguinal hernia occurs as well as congenital anomalies such as hypospadias, cleft palate, cryptorchidism, micrognathia, and mental deficiency. Usually othopedists are consulted for the joint manifestations. The ages of reported cases vary from prematurity to the age of 61 years.

From the above brief survey it is evident that there are many features of arthrogryposis, such as the changes in the articular structures and skin and the occurrence of hernia, all from a very early age, which suggest an ***heritable*** disorder of connective tissue. However, up to 1951 James[60] could find not a single instance of more than one case in the same family. There had been several reports of the disorder in one of twins who appeared to be uniovular.[50,73] These interesting observations cast doubt on both of the two leading theories for the etiology of this condition: (1) an adverse influence of the intrauterine environment; (2) heredity.

Also, to be differentiated from the Hurler syndrome are cleidocranial dysostosis, craniofacial dysostosis of the Crouzon type, Leri's familial plenosteosis[70,114] (to be described in Section VIII), acrocephaly.[88]

The Hurler syndrome was thought to be associated with xanthomatosis and called familial dermo-chondro-corneal dystrophy by François.[40] Rare xanthoma-like lesions were found in the skin in one of my cases (F. M. O'N., Rosewood 4821). Tay-Sachs' disease and the Hurler syndrome bear certain superficial resemblances to each other, and a presumed intermediate form is described by Jervis.[62]

Clinically, cretinism is another frequent misdiagnosis and is often the basis for referral of these cases to endocrinologists. However, the patient with the Hurler syndrome is usually active in his movements and displays normal cutaneous circulation. Tests of thyroid function are usually normal. Bone age is little delayed in the Hurler syndrome and the epiphyseal changes characteristic of cretinism do not occur. Secondary hypothyroidism from involvement of endocrine glands is theoretically possible.

The histologic changes in the brain resemble those of Tay-Sachs' juvenile amaurotic idiocy.[110] The rest of the picture permits differentiation, of course.

Inclusions in the leukocytes said to be indistinguishable from those described in the Hurler syndrome occur as an isolated hereditary trait, the Adler anomaly.[65]

OTHER CONSIDERATIONS

As with the other multifaceted syndromes studied in this series, diverse specialists such as surgeons (*in re:* hernia), otolaryngologists (*in re:* deafness, rhinitis), ophthalmologists (*in re:* corneal abnormality), psychiatrists (*in re:* mental deficiency), cardiologists (*in re:* cardiac abnormalities), orthopedists (*in re:* skeletal deformity) endocrinologists (*in re:* differentiation from cretinism) see these patients for the individual complaints which comprise the total picture.

The nosography of the Hurler syndrome has already begun to follow the pattern of so many other hereditary syndromes: it is at first considered to be largely a pediatric disorder simply because only the most severely affected individuals are identified. These individuals are so severely affected that they are unlikely to survive to adulthood and come to the attention of the internist. Because of the wide variability in expressivity which the student of hereditary disease comes to expect, the occurrence of mildly affected individuals in the adult age group is not surprising. It is entirely reasonable to believe that procreation by these individuals is possible. A 19-year-old patient of Ashby, Stewart, and Watkins was sexually mature.[2] (The authors stated: "Sexual development exceeds the normal.") Mental capacity may be little restricted: one of the patients of Barr and co-workers was an agricultural engineer. Ullrich[112] was one of the first to write in detail about the "late form" of the disease as he called it in contradistinction to the "infantile form." (These are undesirable terms since they may lead to the same confusion which has existed in the case of osteogenesis imperfecta.) He considered it likely that the 47- and 40-year-old patients described by Schmidt in 1938[97] as suffering from "a previously undescribed form of familial degeneration of the cornea in association with osteoarthropathy" and earlier (1927) by Schinz and Furtwängler[95] as "hereditary osteoarthropathy with recessive inheritance," suffered from a mild ("late") form of the Hurler syndrome. Of 11 children of consanguineous parents (first cousins), two daughters had died

at the age of 8 and 18 years, respectively. They showed markedly crippling stiffening of their joints. Scharf[94] described a 28-year-old man, Grebe[43] described patients 21, 24, and 30 years old, Hooper[51] had patients aged 20, 30, and 37 years, and Barr and co-workers[102] had patients 28 and 29 years old. Schwarz and Gagne[98] had a 37-year-old patient who was still living. Zierl[124] reported on a 21-year-old man and Noller[84] on a 43-year-old woman. Cocchi[16] provides two photographs of a patient, one taken when he was 4 years old, the other when he was 22. Cole and associates[19] had a 23-year-old patient.

Hurler[56] stated that mydriasis was unusually marked and prolonged after homatropine but sweating from pilocarpine less than normal.

No definitive treatment for the Hurler syndrome is known. Hurler,[56] in one of her original cases,[58] observed that thyroid extract, while having no measurable effect, produced subjective improvement in the patient. We have observed the same phenomenon (Fig. 3).

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SUMMARY

In the Hurler syndrome, the characteristic features are skeletal deformity, limitation of joint motion, hernia, hepatosplenomegaly, cardiac abnormality, corneal opacification, deafness, and mental retardation.

The basic pathology is the distention of cells of many organs with material of two types: a complex polysaccharide and an aglycolipid. The fundamental defect may concern either the mucopolysaccharide or "structural polysaccharide" of connective tissue.

The Hurler syndrome is usually inherited as an autosomal recessive trait, less commonly as a sex-linked (x-linked) recessive. Clinical differences between the two genotypes appear to exist (see Table I).

Other chondrodystrophies, especially that of Brailsford and Morquio, display many features in common with the Hurler syndrome.

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THE TREPONEMA PALLIDUM IMMOBILIZATION TEST IN THE CEREBROSPINAL FLUID

With a Discussion of the Phenomenon of Chronic Biologic False Positivity in the Cerebrospinal Fluid

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THE specificity of the *Treponema pallidum* immobilization (TPI) test in the blood serum is now well established, and the subject has recently been reviewed.[1] Data concerning this test as applied to spinal fluid are sparse, and so far limited to small groups of patients reported by Nelson and his associates,[2] Durel, Borel, and Louis[3], and in this paper.

In 29 nonsyphilitic persons TPI antibody was not found in the spinal fluid.[2,3]

Table I compares reagin and TPI antibody in the spinal fluids of 219 patients with syphilis. The 58 cases described by Nelson and his group were previously untreated. Of the 121 reported by Durel, Borel, and Louis, some had been treated, others not (numbers not determinable). All 40 of the patients in this series included in Table I had received previous treatment, at intervals of one to thirty years before testing.

If one can accept the results from such small series of patients, it is suggested that in neurosyphilis the TPI antibody is uniformly present in the spinal fluid if the patient is untreated (Nelson). If treatment has been given, TPI antibody may disappear from the fluid as does reagin, and perhaps in a slightly higher proportion of cases (Durel and his associates; this series).

However, in latent syphilis (no clinical symptoms or signs of neurosyphilis, and spinal fluid otherwise completely normal) and whether previously treated or not, the TPI antibody is present in about a quarter of the cases (with surprising uniformity in the 3 series presented). Whether this means that the TPI antibody can cross the choroid plexus-meningeal barrier (as reagin cannot); whether it represents local production of antibody from low-grade invasion of the nervous system by *T. pallidum;* and what significance the finding may have with respect to the eventual development of clinical neurosyphilis: these points are as yet unknown.

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TABLE I. T.P.I. ANTIBODY IN THE SPINAL FLUID AS COMPARED WITH REAGIN

AUTHOR	TYPE OF SYPHILIS	CASES	REAGIN		TPI ANTIBODY	
			PRESENT	ABSENT	PRESENT	ABSENT
Nelson and others[2]	Neurosyphilis	33	33	0	33	0
Durel and others[3]		54	53	1	42	12
This series		26	17	9	20	6
Total		113	103 (91.1%)	10 (8.8%)	95 (84%)	18 (16%)
Nelson[2]	Latent syphilis	25	0	25	6	19
Durel[3]		25	0	25	7	18
This series		11	0	11	4	7
Total		61	0	61 (100%)	17 (27.8%)	44 (72.7%)
Nelson[2]	Other types of symptomatic syphilis early or late	—				
Durel[3]		42	1	41	4	37
This series		3	0	3	0	3
Total		45	1 (2.2%)	44 (97.7%)	4 (8.8%)	40 (11.1%)

The purpose of this paper is in part to record briefly the above facts; and in part to report three cases in which it seems probable that the patients are chronic biologic false positive (BFP) reactors in *both* blood and spinal fluid. No similar examples have so far been published. The case reports follow.

CASE REPORTS

CASE 1.—JHH 540944. A 47-year-old white housewife was first seen in June, 1950, with chief complaint of diplopia of eleven months' duration and tinnitus of the right ear of six months' duration.

Beginning about 1936, she developed intermittent episodes of burning epigastric pain, often radiating to the back, and occasionally associated with vomiting of clear fluid. These attacks were infrequent and usually followed dietary indiscretions. In 1946, she had a sudden onset of ankle swelling and passed a black stool. A duodenal ulcer was demonstrated radiologically. Her standard serologic test for syphilis (STS) was found to be positive. She denied nonmarital sexual exposure, and her three children and husband were determined to be seronegative at this time. From April, 1946, to May, 1947, she received (elsewhere) 27 injections of Mapharsen and 28 injections of bismuth. Her spinal fluid was normal in all respects in June, 1946.

She was placed on an ulcer regimen, which she followed for about six months, and felt well until May, 1949, when she had trouble coordinating her eyes. She developed diplopia in September; and in November, when she consulted an ophthalmologist, it was found that she had a paralysis of the right lateral rectus and right superior oblique muscles. Her spinal fluid now showed an anticomplimentary Wassermann reaction, but was otherwise normal. She received a course of penicillin injections.

In December, 1949, she developed tinnitus in the right ear, with slight impairment of hearing, and vague, nonlocalized headaches. She soon became aware of weakness in the right jaw, and

had some difficulty in forming a bolus of food, and in using her tongue properly. She noted some numbness and occasional pain in the right side of her face.

In April, 1950, she was admitted to a hospital because of massive hematemesis followed by melena. No x-ray films were taken and she was treated with blood transfusions and standard ulcer regimen. About June, 1950, she had another episode of melena and was treated by further transfusions of whole blood.

On her first admission to the Johns Hopkins Hospital in June, 1950, physical examination was within normal limits except for the neurologic findings. There was a vertical and lateral nystagmus of both eyes, and weakness of the right lateral rectus and right superior oblique muscles. There was striking weakness and atrophy of the right temporal and masseter muscles, but no sensory changes in the face. The right fourth and sixth cranial nerves and the motor branch of the right fifth cranial nerve were therefore involved.

Radiograph of the skull showed an irregularity of the contour of the margin of the right anterior clinoid, which was believed to be due to a congenital vascular anomaly. Ventriculogram, pneumoencephalogram and arteriogram were interpreted as normal. Hemogram and urinalysis were normal. The blood STS was positive with a titer of 8 units. The spinal fluid showed no cells; protein content of 42.5 mg. per 100 ml., complement fixation test negative, and colloidal mastic curve flat negative. *TPI tests on both blood serum and spinal fluid were negative.* Fasting blood sugar, nonprotein nitrogen, and serum protein determinations were normal. No L.E. cells were found in the blood. The tentative diagnosis at this time (June, 1950) was intracranial neolasm in a surgically inaccessible location.

In October, 1950, the tinnitus and diplopia became more pronounced. She now noted the development of numbness of the right upper lip and right side of the nose.

In May, 1952 neurologic examination was essentially unchanged. Visual acuity had diminished to 20/30 in the right eye. Radiographs of the skull were now interpreted as showing erosion of the right petrous tip and right foramen ovale. Laboratory studies revealed normal hemogram, blood sugar, nonprotein nitrogen, and serum protein determinations. The cephalin flocculation was ++ in 48 hours (normal 0 to +), the thymol turbidity was 5.5 units and the alkaline phosphatase was 3.7 Bodansky units. The blood STS was still positive in a titer of 32 units. The cerebrospinal fluid now showed no cells, 86 mg. of protein per 100 ml., Wassermann reaction positive with 0.8 and 1 c.c., doubtful with 0.6 ml. and negative with 0.05 to 0.4 ml., and the mastic curve 333-2210000. In view of two previously normal spinal fluid examinations in 1946 and 1950, this was thought perhaps to represent technical error, but examination repeated five days later showed no essential change. It now seemed reasonable to suppose that the lesion was a syphilitic gummatous process at the petrous tip. *However, TPI tests done on two specimens of blood serum and two specimens of spinal fluid obtained on this admission again were reported as negative.*

In December, 1953, she developed rapidly failing vision in the right eye. Examination now revealed pallor of the right optic disc and involvement of the sensory (as well as the motor) branch of the right trigeminal nerve. Radiographs of the skull showed more extensive erosion of the right petrous pyramid, and of the right middle fossa. A right carotid angiogram was interpreted as showing elevation of the middle cerebral artery and straightening of the siphon. The blood STS was still positive in a titer of 64 units. The spinal fluid complement fixation reaction was again positive with 0.1 c.c.; but *TPI tests on blood and spinal fluid were again negative.* A right temporal craniotomy was performed and a large glioma was found extending from the petrous bone anteriorly to the superior orbital fossa.

Summary.—This patient, whose blood STS had been known to be strongly positive for eighteen years (1936-1954), has been TPI negative as to blood serum on four occasions. Her spinal fluid, normal by standard tests in 1946 and 1950, has shown the presence of reagin on four occasions since 1952; but the TPI test on the fluid has been negative three times. Her neurologic disorder was proved to be due to a histologically verified glioma; but she has continued to have major episodes of hematemesis in only the first of which (1946) was there any radiologic evidence of an intrinsic lesion in the gastrointestinal tract. All subsequent radiologic examinations have been negative.

Is she a BFP reactor in both blood and spinal fluid; and if so, what is the cause of the BFP reaction?

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CASE 2.—A 61-year-old white man from Israel entered the Baltimore Eye and Ear Hospital in February, 1953, on the service of Dr. Jonas Friedenwald because of progressive ocular proptosis of eighteen months' duration.

There was no family history of syphilis. His wife and two sons, whose STS had been repeatedly negative, were frequent blood donors.

The patient had enjoyed good health until two years previously when he fell and struck the head of the left ulna. There subsequently developed regional erythema, pain, and probable cellulitis which was treated with many injections of penicillin during a period of two weeks. Eighteen months prior to admission he noted a small swelling in the inner canthus of his right eye lid. The lesion progressed, and both eyes became noticeably proptosed. In November, 1951, the patient entered a hospital in Haifa for diagnostic study. Blood STS and three cerebrospinal fluid examinations were reported to have been negative. Radiographs of the skull and gastrointestinal tract were interpreted as normal. Radiation therapy was given to the region of the orbits, without effect on the proptosis. Thereafter, a course of cortisone therapy was also of no benefit.

Physical examination in February, 1953, showed little except extreme bilateral exophthalmos, more marked on the left. The pupils were round, regular and equal. They reacted sluggishly to light and normally to accommodation. There was early left optic atrophy, and a left orbital decompression was done. Biopsy of the tissue removed was reported as "chronic inflammatory tissue."

The STS was positive in a titer of 8 units. Serum cholesterol was 217 mg. per ml., total serum protein 7.4 Gm., albumin 4.0 Gm., and globulin 3.4 Gm. per ml.; cephalin flocculation was 3+ at 24 hours and 4+ at 48 hours, and the thymol turbidity was 16.3 units. The cerebrospinal fluid contained 2 cells; 79.9 mg. per 100 ml. of protein; the complement fixation reaction was positive from 0.4 to 1.0 ml., and negative at 0.025 to 0.2 ml. The mastic curve was 4443321000. *The TPI tests on two specimens of blood and two of cerebrospinal fluid were negative.*

The diagnosis of gummatous lesion of the orbit was considered but doubted because the process was bilateral, an unusual occurrence in this type of late syphilis. Penicillin therapy for ten days, followed by ten injections of Mapharsen, 40 mg. each, brought about no improvement. Because some granulomatous lesions of the orbit were believed to be related to collagen vascular disease, the patient was treated with intravenous corticotropin for five weeks, resulting in a dramatic disappearance of the exophthalmos.

When the patient was last seen in May, 1953, there was no recurrence of exophthalmos. The blood STS remained positive. Total serum proteins were normal, cephalin flocculation 1+, thymol turbidity 2.5 units. The cerebrospinal fluid now contained no cells; 90.6 mg. of protein per 100 ml.; the complement fixation reaction was still positive with 0.6 to 1.0 ml., doubtful with 0.2 to 0.4 ml., and negative with 0.025 ml.; mastic curve 4432110000. *The TPI test was again negative with both blood and spinal fluid.*

Summary.—This patient, with granulomas of the orbits of undetermined etiology, is an apparent BFP reactor both in blood and spinal fluid.

CASE 3.—JHH 453439. A 46-year-old white man was seen in 1947 because of visual impairment in the right eye.

In 1942 he noted that objects seemed to have a brown hue. He stopped smoking and his vision returned to normal. In 1945, when his visual acuity again became poor, he was seen by an ophthalmologist who described retinal periphlebitis in the right eye with numerous intraretinal and preretinal hemorrhages. The left eye was normal. The blood STS was weakly positive. Examination of the cerebrospinal fluid showed a positive Pandy test, negative complement fixation reaction, and a mastic curve of 5533210000 (cell count not done). After a course of two million units of penicillin, there was subjective improvement in vision but no objective change in the eye grounds.

Because of a recurrence of the same visual trouble, the patient was referred for consultation in December, 1947. Physical examination was normal except for the ocular findings which showed bilateral anterior uveitis, posterior corneal deposits, and nodular retinal lesions suggestive of sarcoidosis. STS was still positive with a titer of 4 units; the spinal fluid showed 47 lymphocytes, and 100.5 mg. of protein per 100 ml.; complement fixation reaction was negative; mastic curve

5554322000. Serum proteins were within normal limits. No L.E. cells were found in the blood. Radiograph of the chest and air encephalogram were normal. Biopsy of a cervical lymph node was reported as normal. Brucella agglutination tests were negative. The patient received two courses of penicillin and sulfadiazine therapy without effect on the lesions.

In 1949, attempts to demonstrate a virus in the cerebrospinal fluid by inoculation of mice and chick embryos were negative.

He received protracted courses of Aureomycin and p-aminosalicylic acid from 1949 to 1951 because of recurrent exacerbations of the ocular disease. The patient felt that remissions and exacerbations were unrelated to drug therapy. In March, 1951, visual acuity in the right eye was 20/70, in the left eye, 20/20.

Since it was believed that the most probable diagnosis was sarcoidosis, the patient was given 200 mg. of cortisone daily for eighteen days in July, 1951, and he was subsequently continued on maintenance dosage. Both objective and subjective improvement were striking. The ocular lesion cleared and visual acuity in the right eye increased to 20/30. Spinal fluid examinations during the course of cortisone therapy showed improvement in the cell count, protein, and mastic curve. The spinal fluid Wassermann reaction had always been negative in large (1.0 ml.) amounts. In October, 1951, when the dose of cortisone was 25 mg. daily, fresh retinal lesions appeared in the left eye. These lesions all resolved on increasing the dosage of cortisone to 200 mg. daily. When the dosage of cortisone was again reduced to 50 mg. daily, a relapse occurred, but there was gradual improvement when the dose was raised to 75 mg. daily. There was slow improvement until March, 1952, when a fresh hemorrhage appeared in the left eye, obscuring the disc and macula. Diminution of vision and anterior uveitis occurred in the right eye.

The patient was then admitted to The Johns Hopkins Hospital. The blood STS was negative. Serum protein, calcium, phosphorus, and alkaline phosphatase were within normal limits. Examination of spinal fluid revealed 52 lymphocytes; protein 54 mg. per 100 ml.; negative complement fixation reaction. Investigations for toxoplasmosis, torula, and other fungi were not revealing. The L.E. cell preparation was negative. Radiographs of the skull were negative, and those of the chest showed slight enlargement of the left ventricle.

Intravenous corticotropin was given daily for three weeks. Eight days after beginning of therapy there was clearing of the anterior uveitis in the right eye and considerable resolution of the hemorrhage in the left eye. There was improvement in visual acuity bilaterally. The patient was discharged to take corticotropin gel 40 to 80 mg. daily.

It is interesting to note that the STS became negative during cortisone therapy and remained so thereafter.

TPI tests on the blood serum were negative in 1950, 1951, 1953, and on the spinal fluid were negative in 1949 and 1953.

Summary.—This patient is known to have pleocytosis (range 50 to 150 lymphocytes), excess protein content (range 50 to 200 mg. per 100 ml.), first zone colloidal curve, and negative complement fixation reactions in the spinal fluid on many occasions for ten years. His neurologic status is still entirely normal. No definitive diagnosis of the ocular lesion has been made. Does he have sarcoidosis of the eyes and nervous system, with associated BFP reaction in the blood and in the spinal fluid?

DISCUSSION

The three patients whose case reports have been presented are considered to represent biologic false positivity in both the blood serum and the cerebrospinal fluid. All three patients had received antisyphilitic therapy one to four years prior to the performance of the TPI test. The possibility of technically false positive standard serologic reactions has been definitely excluded through the demonstration of reagin in the blood and abnormalities of the cerebrospinal fluid on multiple occasions. It is most unlikely that any of these individuals

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has, or ever had, syphilis, since there were unequivocably negative TPI tests on the blood serum and cerebrospinal fluid in each patient on at least two specimens. In no patient was there epidemiologic or clinical evidence of syphilis. It is likely that a common denominator in these three patients is an alteration in the protein content of the cerebrospinal fluid, particularly the globulin component, resulting in reagin-like activity.

An elevated cerebrospinal fluid protein level is frequently seen in the presence of brain tumor, and possibly furnishes the explanation for the false positive reaction in the spinal fluid in Case 1, but this could not account for the false positive test for syphilis in the serum. It is possible that this patient is a chronic biologic false positive reactor, who, coincidentally, had a brain tumor.

Although it has not been proved, it is possible that collagen vascular disease may be the underlying disease process in Case 2. Attention has already been directed by Moore and Mohr,[5] and Moore and Lutz[6] to the relationship of the chronic biologic false positive reaction in the blood serum to collagen vascular disease.

If Case 3 is indeed Boeck's sarcoid, we may assume that globulin alterations commonly associated with this disease, although not detectable by the gross quantitative techniques routinely employed, were responsible for the false positive reaction.

The rare phenomenon of biologic false positivity in the spinal fluid has been known for many years (but not verified by negative TPI tests). Previously described cases of false positivity have generally been associated with infectious or inflammatory processes, involving the central nervous system, or secondary to the contamination of spinal fluid with seropositive blood, or due to technical error. The biologic false positive reactions in the cerebrospinal fluid reported to date have all been of the acute type; i.e., associated with infection or inflammation of the central nervous system. The acute BFP reaction almost universally reverts to negative with resolution of the underlying disease process.

Nonne[7] in 1913 mentioned a case of false positive Wassermann in the spinal fluid in association with scarlatina. He thought that false positive tests occurred in some tropical diseases such as leprosy and malaria. Dickson[8] in 1937, described false positive tests in the spinal fluid. In 1940, Worster-Drought[9] suggested that the use of a Wassermann technique of too great sensitivity would frequently cause false positive tests.

Moore[10] stated, in 1941, that a positive Wassermann or flocculation test in the cerebrospinal fluid is almost absolute evidence of syphilitic involvement of the central nervous system, but pointed out the occurrence of false positive reactions in some cases of aseptic (lymphocytic) meningitis and in acute pyogenic meningitis. Characteristic of this phenomenon is reversion of the spinal fluid to seronegativity following the subsidence of the inflammatory process. Scott, Reynolds, and Mohr[11] in 1942 reported eight cases of meningitis in which there were false positive tests in the cerebrospinal fluid. Three of their patients had tuberculous meningitis with seronegative serum but with reagin in the spinal fluid. Two cases were of meningococcal meningitis, with seronegativity in the serum and with positive spinal fluid Wassermann reactions. Of their

three patients with aseptic choriomeningitis, all had positive spinal fluid Wassermann reactions; two had seronegative and one had seropositive serum. This latter patient was thought to represent a reagin transfer through the cerebrospinal fluid barriers, because seventeen days after admission reagin could no longer be demonstrated in the spinal fluid.

In 1946 Merritt, Adams, and Solomon[12] reported that biologic false positive Wassermann reactions in the spinal fluid rarely occurred. They suggested leprosy, trypanosomiasis, and cerebral malaria as possible causes. They proposed that perhaps the chief reason for false positive tests in the spinal fluid is poor technique either in the actual performance of the test or improper labeling of specimens. The presence of large amounts of reagin-containing serum in the spinal fluid, such as may occur in cerebral vascular hemorrhage, subarachnoid block or purulent meningitis, may be responsible for confusion. Merritt and Fremont-Smith,[13] in their monograph, reach essentially the same conclusion.

In our three cases demonstrating *chronic* BFP reactions in the cerebrospinal fluid, a mechanism, not previously described in the spinal fluid, must be responsible for this phenomenon. It must be presumed that a chronic nonsyphilitic disease process resulted in the appearance in blood serum and spinal fluid of a reagin-like substance which was capable of reacting with standard Wassermann antigens. It is further presumed that chronic BFP reactions in spinal fluid, like BFP reactions in serum, are a manifestation of tissue injury.[6]

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SUMMARY

This study reports the experience with the TPI test in the cerebrospinal fluid of 43 patients in the diagnostic categories of early syphilis, latent syphilis, neurosyphilis, and biologic false positive reactions, and correlates our results with those reported by other authors.

The behavior of the TPI antibody in central nervous system syphilis appears to be similar to that of reagin. In latent syphilis there is disagreement between the two tests, in that there are patients with latent syphilis who have the TPI antibody in otherwise normal spinal fluids. It is probable that patients with latent syphilis who have demonstrable TPI antibody in the cerebrospinal fluid may be reclassified as a type of asymptomatic neurosyphilis. The precise significance of this phenomenon is as yet unknown, and the prognosis of such patients has not yet been established.

Three patients are presented with chronic biologic false positive reactions in both blood serum and cerebrospinal fluid. It is suggested that alterations in the globulin fraction of the spinal fluid, probably secondary to tissue injury, are responsible for the false positive reactions, since these patients had brain tumor, probable collagen vascular disease, and probable sarcoidosis, respectively.

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Review

THE APPLICATION OF RESPIRATORY PHYSIOLOGY TO THERAPEUTIC PROCEDURES IN PULMONARY EMPHYSEMA

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INTRODUCTION

THE administration of oxygen is employed in patients with pulmonary emphysema for the treatment of impaired respiratory function due to alveolar overdistention and bronchial constriction, cardiac insufficiency associated with failure of the right or left heart or both, and decreased pulmonary reserve associated with loss of physical fitness; oxygen is used intermittently in the latter instance during walking in a graded exercise program. Since serious interference with the diffusion of oxygen and carbon dioxide occurs more commonly in pulmonary emphysema than in any other chronic illness, the factors responsible for impairment of respiratory function will be carefully appraised by our various contributors. In this chapter the consequences of the disturbed pulmonary physiology, including especially hypoxia, are outlined as a background for the administration of oxygen and helium-oxygen mixtures; certain additional aspects of the mechanism of dyspnea are described as a basis for other forms of physiologically directed therapy, such as the clinical application of pressure breathing.

Both acute and chronic arterial hypoxia occurs in the majority of cases of pulmonary emphysema, manifested by a lowered oxygen saturation of the arterial blood, or by a therapeutic response to oxygen inhalation at rest or after exercise. In addition to a long-standing type of oxygen want, more severe acute hypoxia takes place at times as a result of bronchopulmonary infections and exacerbation of bronchospasm. Since hypoxia, a term considered more accurate to describe a lowered tension of oxygen in the tissues than anoxia, is so character-

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istic of this clinical entity, the effects of abrupt deprivation of oxygen on the human individual will be appraised from the standpoint of the uncomplicated syndrome of acute hypoxia, which has been clarified through experiments on men and animals exposed either to a diminished pressure or concentration of oxygen in the inhaled atmosphere.

PATHOLOGIC CHANGES RESULTING FROM ACUTE HYPOXIA

Although it has been long recognized that the central nervous system is especially vulnerable to hypoxia, studies on the gradient of reaction in different parts of the brain have revealed that the small pyramidal cells of the cortex are far more sensitive than the medulla and spinal cord. The cerebral cortex may manifest severe damage as a result of hypoxia maintained for 2 to 10 minutes, depending upon the experimental technique employed; furthermore, Morrison found that the frontal lobe cortex was more readily damaged by graded hypoxia than the rest of the brain cortex and other parts of the central nervous system. The available evidence strongly supports the assumption that the more recently developed elements in the central nervous system are more sensitive to injury, possibly because they require a higher oxygen consumption for maintenance of normal function.

Cerebral hypoxia can be produced not only by the production of a lowered tension of oxygen in the tissues of the body but also, as Schmidt and his colleagues have shown, by a local increase in the oxygen uptake of the brain beyond the capacity of the existing oxygen supply, as revealed by the high oxygen consumption of brain cells after administration of convulsive drugs. The cerebral oxygen uptake in many instances varies directly with the degree of cerebral activity. The physiologic limits of oxygen consumption of the brain are described as being from one-half to double the resting value.

The *heart* apparently is the organ next most sensitive to oxygen want. The myocardial lesions from oxygen want are focal in distribution and found most prominently in the papillary muscle and the left ventricular wall. Greater damage is experienced by older animals than young ones as a result of acute hypoxia.

The effects of long-continued hypoxia on the *lungs* themselves are of considerable interest. As is well known, capillaries undergo an increase in permeability to serum after exposure to anoxia. When inhalation of 10 per cent oxygen was combined with inspiration under negative pressure, produced by resistance in the trachea, more pulmonary congestion and intra-alveolar edema were noted by Drinker than took place when similar pathologic states were produced by inspiratory obstruction alone (Moore and Binger, Kernan and Barach). When serum escapes from the capillaries into the alveoli at a greater rate than can be absorbed by the lymphatics or, in an unconscious subject, removed by coughing, it accumulates within the alveoli. During periods of obstruction of the bronchioles, either partial or complete, the local hypoxia produced would therefore tend to promote localized formation of edema. The application of this concept to patients with chronic obstructive pulmonary emphysema leads to an interesting speculation concerning the cause of the increased sputum which is commonly

found at night and expectorated in the morning. The decrease in pulmonary ventilation during sleep may result in areas of severe alveolar anoxia with a consequent increase in capillary permeability and transudation of serum into the alveoli. As will be referred to again later, when patients with this disorder reside continuously in an oxygen enriched atmosphere, a conspicuous result of treatment is the prompt decrease and, at times, disappearance of expectoration.

The *adrenal gland* also is sensitive to hypoxia; animals exposed to a diminished pressure of oxygen have shown a decrease in adrenal ascorbic acid and lipid. An increase in 17- and 11 ketosteroids takes place as a result of acute oxygen want in man, with a diminished tolerance for glucose and a decrease in circulating eosinophils. In contrast to the effect of hypoxia on oxygen-sensitive organs, the *blood supply to the extremities* may be cut off by a tourniquet for several hours without injury to the tissues of legs.

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PATHOLOGIC PHYSIOLOGY OF HYPOXIA

The acute disturbance in the physiology of the patient with pulmonary emphysema due to the abrupt onset of hypoxia may be understood best by noting the effects on normal human subjects of a decreased pressure of oxygen at high altitude. A mistake not uncommonly made in clinical practice is to attribute the manifestations of acute oxygen want to other factors of the illness, even to bad behavior, rather than to lack of oxygen. Since pathologic studies on organ sensitivity to hypoxia revealed that the brain was the most vulnerable and the heart the next most quickly affected, the disorder in the *functioning* of the human organism was correctly assumed to proceed in a similar manner. During World War II, extensive studies of the effect on aviators of abrupt ascent to simulated high altitude resulted in a precise formulation of the consequences of uncomplicated hypoxia. Since these investigations provided information of a qualitative and quantitative nature concerning the consequences of oxygen want of the degree found in cases of pulmonary emphysema, a brief review of some of the pertinent findings will be presented.

Physical Factors Involved in the Production of Altitude Hypoxia.—At 18,000 feet the atmospheric pressure is reduced from 760 mm. Hg to 380 mm. Hg, or one-half the sea level pressure. One liter of gas at this altitude would have expanded in a free state to 2 liters; the expanded volume would hold the same number of oxygen and nitrogen molecules as were present at sea level, but each molecule would be separated from every other one by a greater distance. The inspired air at 18,000 feet would appear at first glance to contain one-half the number of oxygen molecules as were present in the inhaled air at sea level, but in actual fact the pressure of oxygen in the lungs is considerably less than one-half the sea level pressure because of the following consideration.

Carbon dioxide and water vapor in the alveoli, both of which are formed constantly in the lungs, occupy space that prevents inhalation of air from outside the body. In order to determine accurately the tension of oxygen in the lungs at 18,000 feet, i.e., 380 mm. Hg, the following calculation is undertaken: $(380\text{-}47) \times 0.209$, the percentage of oxygen in a saturated atmosphere, will give the inspired oxygen pressure. The pressure of water vapor in the lungs is 47 mm.

Hg, and that of carbon dioxide at sea level is 40 mm. Hg. However, an individual exposed to acute hypoxia, such as would exist at 18,000 feet, would increase markedly the volume of breathing with the result that additional carbon dioxide would be blown off, and the pressure of CO_2 would be replaced by an equivalent pressure of oxygen. The actual tension of oxygen in the alveoli might then be (380-47) × 0.209 minus 30 (if this was in fact the lowered carbon dioxide pressure) or 39.6 mm. Hg. The respiratory quotient of 1 is assumed in these calculations.

The alveolar oxygen pressure in a normal individual at sea level is about 100 mm. Hg, which is sufficient to saturate the hemoglobin in the red cells to 98 per cent. At an altitude of 18,000 feet, a pressure of 39.6 mm. Hg obviously will not provide the tissues with the accustomed pressure of oxygen, with the result that the function of the various organs, especially the brain and the heart, are seriously interfered with. This degree of hypoxia is equivalent to that produced by inhalation of approximately 10 per cent oxygen with 90 per cent nitrogen. As a result of the increased pulmonary ventilation and the loss of CO_2, the acid base equilibrium shifts toward the alkaline side to a considerable extent, such as a change in pH of 7.42 to 7.55, due to a relatively more rapid elimination of carbon dioxide in proportion to the adaptive reduction in the total base ions in the blood.

In Fig. 1 the effect of decreasing barometric pressures is shown at various

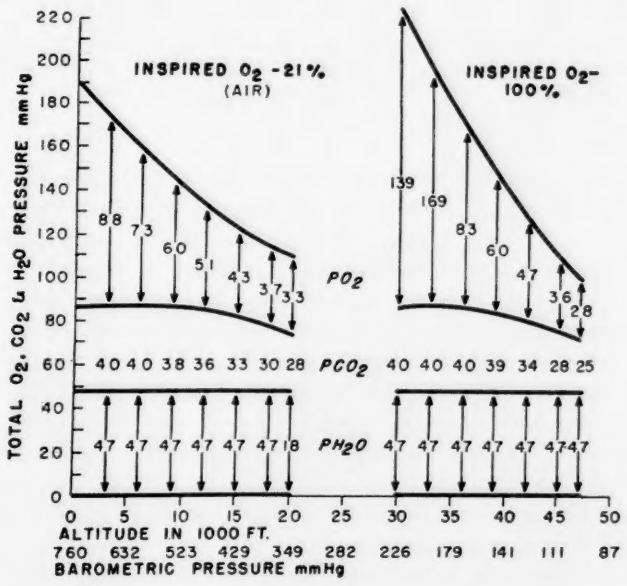

Fig. 1. Effect of altitude hypoxia on alveolar oxygen and carbon dioxide pressure in normal subjects breathing air to 20,000 feet and 100 per cent oxygen to 40,000 feet. Vapor pressure of 47 mm. Hg is constant in each instance.

altitudes. The vapor pressure of water is governed by the ambient temperature and not ambient pressure. The temperature within the lung of individuals subjected to an 18,000 feet altitude remains the same as at sea level in spite of a decrease in ambient pressure of 50 per cent. Thus, the number of oxygen molecules in any given volume remains the same at sea level as at 18,000 feet. The increased ventilatory response to hypoxia is followed by a progressive loss of carbon dioxide which leads to varying degrees of alkalosis.

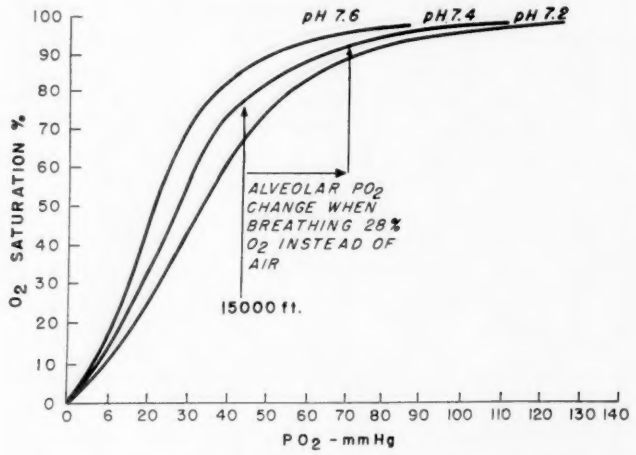

Fig. 2. Dissociation curves in alveolar oxygen pressure is produced by an increase from 21 to 28 per cent in inspired oxygen in the normal individual exposed to 15,000 feet, as a result of the steep slope of the curve in this area. A rise of 7 per cent oxygen at this altitude is equivalent to about 3.5 per cent at sea level.

The harmful effects of the hyperventilation alkalosis induced by acute hypoxia was revealed in a study of the physiologic action of 10 per cent oxygen inhalation with and without carbon dioxide in cases of coronary sclerosis and normal individuals (Barach, Steiner, Eckman, and Molomut). The electrocardiographic signs of coronary insufficiency produced by inhalation of 10 per cent oxygen-nitrogen mixtures for 10 to 20 minutes were found to be prevented by the addition of 2 per cent carbon dioxide. It was interesting to note that the pH of the arterial blood was 7.46 after inhalations of the low oxygen-carbon dioxide mixtures and 7.52 after the inhalation of 10 per cent oxygen without carbon dioxide. Furthermore, precordial distress did not occur when the low oxygen mixture was breathed together with carbon dioxide, but appeared when low oxygen mixtures alone were inhaled. It was also observed that the depression of T wave and S-T segment produced by uncomplicated hypoxia was prevented when carbon dioxide was added to a 9 per cent oxygen mixture. The arterial oxygen saturation produced by this degree of hypoxia varied from 57 to 88 per cent. These results appeared to indicate that the alkaline shift caused by acute hypoxia resulted in constriction of the capillary bed, additional ischemia, and progressively increased hypoxia of the cardiac muscle since alkalosis itself results

in oxygen being held more firmly to the hemoglobin. When the small concentration of CO_2 was added, the oxygen tension in the cardiac muscle was presumably higher because of the absence of alkalosis. This may have played a significant role in producing a higher T wave since it was shown that inhalation of 100 per cent oxygen itself was followed, in the majority of cases, by an increased height in the T waves.

In Fig. 2, the dissociation curves of hemoglobin reveal the characteristic lowering of the arterial oxygen pressure at a given oxygen saturation when the pH becomes alkaline. The effect of a small increase in oxygen percentage of the inspired air, i.e., from 21 to 28 per cent results in a relatively large rise in alveolar oxygen pressure when hypoxia is severe, because of the steep slope of the curve in this region, at 15,000 feet a 7 per cent increase in inspired oxygen is equivalent to approximately 3.5 per cent at sea level.

SYMPTOMS AND SIGNS OF HYPOXIA

Early manifestations of disturbance in the physiology of the human organism as a result of mild oxygen want, such as takes place after several hours at altitudes between 7,000 and 10,000 feet, are a decrease in the peripheral field of vision and dark adaptation, and increase in pulse rate. A significant impairment in emotional control occurs at 12,000 feet. An increase in pulmonary ventilation at 12,000 feet results in a blowing off of carbon dioxide which is gradually compensated for by a corresponding reduction in the sodium bicarbonate level of the blood, a lessened secretion of acid in the urine, and an increase of chloride ions in the blood.

The arterial oxygen saturation at 10,000 feet is approximately 90 per cent, and at an altitude of 15,000 feet this is lowered still further to 78 per cent. At the latter altitude, although the oxygen saturation is lowered 20 per cent, the tension of oxygen in the blood may be only 41 mm. Hg, or less than half normal. In clinical discussions concerning the factor of hypoxia in the production of dyspnea, in pulmonary emphysema a slight lowering of the arterial oxygen saturation is at times regarded, quite erroneously, as being of little significance. A decrease in tissue oxygen pressure results in a burdensome elevation of the pulmonary ventilation in these subjects, as will be seen later.

After several hours exposure to altitudes of 12,000 to 14,000 feet, other characteristic symptoms appear, such as headache, nausea, and lassitude. In respect to mental function, impairment of emotional control is one of the earliest and most conspicuous responses to hypoxia. In some individuals, overconfidence, euphoria, exaggerated self-esteem, and boisterousness are outstanding manifestations of a decreased activity of the inhibitory or critical functions of the brain. This is of considerable interest since the frontal lobe cortex has been found to be damaged by hypoxia before other parts of the brain. In other cases, dullness, drowsiness, irritability, and anger are observed. Depending upon the environment in which the effects of hypoxia are tested, impairment of emotional control may manifest itself in the inability to inhibit aggressive, sexual, or egoistic impulses. In fact, the effects of hypoxia, as induced by decreased tension of the oxygen in the atmosphere, were found by McFarland and Barach to be

astonishingly similar to those resulting from alcohol, provided environmental factors were made similar in each case.

Although human subjects at an altitude of 12,000 feet generally revealed good performance in neuromuscular tests, this efficiency was shown to be strikingly imparied when remarks were made which challenged the emotional adjustment of the subject, such as irritating statements about his personality. Men who withstood criticism blandly at sea level reacted with violent hostility during exposure to moderate hypoxia in a low pressure chamber. The importance of this response in civil and military aviation is difficult to overestimate; but it should be recognized also that a similar state frequently exists in patients with pulmonary emphysema in whom a comparable degree of impairment of respiratory function takes place. Often patients are judged adversely because of apparently immature behavior that is not characteristic of their personalities during periods when they are free from hypoxia.

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When lack of oxygen is severe, the pulse rate becomes more rapid, breathing is accelerated, consciousness is rapidly impaired and finally lost as a result of damage to the central nervous system, heart, and other organs.

Although the brain is the organ whose function is impaired most significantly by acute hypoxia, the disturbance in function of the heart is revealed not only by the increase in pulse rate but also by a characteristic depression of the T wave of the electrocardiogram. At an altitude of 15,000 feet, or during inhalation of a 12 per cent oxygen mixture, the electrocardiogram shows this characteristic change. As is now well known, patients with coronary artery disease during inhalation of 10 to 12 per cent oxygen frequently manifest not only depression of the T wave but also changes in the S-T segment which confirm or establish the diagnosis of coronary insufficiency. The hyperventilation induced by hypoxia and lowered CO_2 tension plays a role in T-wave depression since the addition of 2 per cent CO_2 to the low oxygen mixture frequently prevents T wave change, as has been previously discussed. Acute coronary insufficiency may be precipitated by inhalation of 10 per cent oxygen, but the symptoms produced are counteracted by prompt inhalation of 100 per cent oxygen. With severe hypoxia the heart is dilated, the degree depending upon the severity and duration or oxygen deprivation.

The increase in pulse rate is a highly characteristic sign of acute hypoxia; this tachycardia represents an increased blood flow when the arterial oxygen saturation is in the neighborhood of 80 per cent (Asmussen and Chiodi). In studies of the circulation with the Fick technique, Cournand, Richards, and their collaborators observed a rise in pulmonary artery pressure as a result of inhalation of 10 per cent oxygen atmospheres. The bearing of this finding on cor pulmonale is of considerable interest, since the right ventricular systolic pressure is increased in these patients, at times from 22 to 88 mm. Hg.

The high susceptibility of the liver and kidneys to hypoxia has been shown by Schorr and his collaborators, who found that a vasodepressor material was elaborated by the liver in shock, and that a vasoexcitor material produced normally by the kidney was stopped by prolonged hypoxia such as occurs in shock. In a study of the circulation in human shock by Cournand and others, the cardiac

output, as determined by the direct Fick technique, was lowered one-third in some cases with an increase in blood lactic acid, a shift in pH to the acid side, and a fall in oxygen saturation of the mixed venous blood from 65 to 35 per cent, and, in severe cases, to as low as 15 per cent. In addition to the treatment of shock by administration of intravenous fluids to overcome the discrepancy between the diminished circulating blood volume and the relatively large vascular bed, inhalation of oxygen has been employed. In experimental hemorrhagic shock in dogs, the content of oxygen in arterial, femoral vein and right heart blood has been shown to be substantially increased when 100 per cent oxygen was breathed, i.e., 1.5 c.c. of oxygen per 100 c.c. of blood.

When the onset of hypoxia is more gradual and sustained in patients with pulmonary emphysema, the resultant effects are more comparable to the consequences of residence at high mountainous places; thus Heber, in discussing the symptoms of the average European at Ladak Kashmir (11,500 ft.,) says: "The feeling of fitness on arrival soon gives way to a terrible weariness and restlessness, especially after a short day of mental work. The mental deterioration is not as serious, however, as the change in temperament and all subjective functions. It is astonishing how the most decisive of men will slowly and insidiously lose the power of decision and become unwilling to bear responsibility." Barcroft noted the increase in fatigability at Cerro de Pasco (14,200 feet) and the inevitable slowness and clumsiness at all work. In the clock test it took him twice as long to read the reverse face of the clock as it did at sea level. He remarked that any prolonged mental effort usually involved a degree of fatigue which necessitated a trip to the coast to prevent a "nervous breakdown."

The inertia so commonly observed in patients with chronic pulmonary emphysema may well be due, at least in part, to the persistence of long-standing hypoxia, although acclimatization tends to modify the severity of reaction to some extent, as will be discussed later.

CHANGES INDUCED BY RELIEF OF HYPOXIA IN PULMONARY EMPHYSEMA

When chronic arterial hypoxia was suddenly terminated by inhalation of 50 per cent oxygen, striking changes in mental function were observed to occur in a period of one hour to one day; in the early studies of Richards and the author on administration of oxygen to patients with chronic heart disease, a subdued state was frequently encountered, together with a tendency for increased sleep; but an abrupt precipation of an irrational, comatose state was observed at times in patients with chronic pulmonary emphysema. In 1938, I reported that this reaction took place in those patients who were abruptly treated with high concentrations of oxygen (i.e., 40 to 50 per cent oxygen atmospheres) and that it could be prevented by a program of administering gradually increasing oxygen concentrations. In the paper "Impairment in Emotional Control Produced Both by Lowering and Raising the Oxygen Pressure in the Atmosphere," I mentioned that this extraordinary psychologic change might be due to the increase of blood carbon dioxide which was produced by the diminished volume of breathing that Richards and I had demonstrated to be the characteristic consequence of inhalation of 50 per cent oxygen in cases of cardiac failure and

especially chronic pulmonary emphysema. When the phenomenon of increased CO_2 levels in the blood was emphasized as a cause of the comatose state by Comroe and others, I had arrived at the opinion that the increase in CO_2 tension only produced irrationality when it was accompanied by a change in pH, with a true respiratory acidosis. The effects of the sudden reversal of hypoxia induced by oxygen inhalation in patients with pulmonary emphysema, especially in respect to change in mental function, were described as follows in the paper referred to above:

> In those cases of pulmonary emphysema in which pre-existing arterial anoxemia has been present over a considerable period of time, the continuous ad ministration of 50 per cent oxygen may result in a swift impairment in emotional control, proceeding to delirium in some instances. This is also true of the inhalation of oxygen in patients with cerebral arteriosclerotic disease in which the brain may be assumed to suffer from pre-existing ischemic cellular anoxia. In both groups of patients inhalation of high oxygen atmospheres, such as is provided by residence in a tent or oxygen room, may be followed by depression, crying spells, drowiness, sleep, coma, or delirium.
>
> In a case of pulmonary emphysema, with moderately severe arterial anoxemia, inhalation of oxygen resulted in relief of dyspnea and cyanosis, and also in relapse into a comatose state which lasted six days. At the end of this period the patient awoke cheerful, rational, and alert. Before treatment he had been apprehensive and depressed for several years; following oxygen treatment he was optimistic and unworried as long as the oxygen concentration in the atmosphere was not reduced. In a women with cerebral arteriosclerotic desease, an irrational state began within five hours after inhalation of 50 per cent oxygen. Active delirium was once observed in a man with chronic anoxia due to pulmonary emphysema after he had been in an oxygen tent for a period of one hour. His arterial oxygen saturation had been 57 per cent prior to treatment.
>
> In patients with chronic anoxia, the personality of the individual may appear normal before inhalation of oxygen, and swiftly undergo a profound change. It is my impression that the first effect of breathing oxygen is a subdued state in the majority of cases. I cannot, in this paper, discuss the metabolic consequences of altering the oxygen tension in these cases but it may be briefly reported that an increase in the content of carbon dioxide in the blood takes place whenever the volume of breathing is diminished by inhalation of oxygen. Whether the initial depressed state is related to this effect, or to other more complex changes, cannot now be decided.

The significance of retention of CO_2 following administration of various concentrations of oxygen will be discussed later; but the clinical value of the adaptation response to administration of gradually increasing oxygen concentrations has been confirmed many times since 1938 by Barach, Bickerman, Beck, Segal, and, more recently, by Simpson. It has become steadily more clear as a result of the studies of Schmidt, Comroe, and others, that the patient with pulmonary emphysema was peculiarly dependent upon the chemoreceptors in respect to the regulation of the volume of breathing rather than arterial CO_2 tension, or pH stimulation of the respiratory center.

SENSITIVITY OF THE CHEMORECEPTORS TO ARTERIAL HYPOXIA

The receptors of the carotid and aortic bodies are stimulated mainly by decrease in arterial oxygen tension, which is the organism's chief defense against hypoxia because of the resultant increase in pulmonary ventilation. These chemoreceptors should be distinguished from the receptors of the carotid sinus and

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aortic arch, which respond to alterations in arterial blood pressure. In normal human subjects the chemoreceptors are not stimulated until the oxygen in the inspired air is lowered to 18 per cent. In fact, the volume of breathing is not increased significantly until altitudes of 8,000 to 10,000 feet are obtained, corresponding to an arterial oxygen saturation of approximately 90 per cent. As hypoxia is increased, however, there is a progressive rise in pulmonary ventilation as a result of stimulation of these chemoreceptors, with a consequent decrease in blood carbon dioxide tension and a shift in the acid base equilibrium to the alkaline side. More severe lack of oxygen impairs the function of the medullary center of the brain, produces respiratory depression and an acidosis due to carbon dioxide retention and failure of adequate oxidation of the products of metabolism.

Although only a slight increase in breathing occurs in the normal subject at an arterial oxygen concentration of 90 per cent, the view that hypoxia of this degree does not play a significant role in the dyspnea of congestive failure (Harrison and associates) and pulmonary emphysema (Baldwin and co-workers) is at variance with the response of these patients to oxygen inhalation; hypoxia in congestive failure and pulmonary emphysema has been shown to be of crucial importance in maintaining dyspnea, even in cases in which the arterial oxygen saturation is lowered to this slight extent, i.e., to between 90 and 93 per cent (Barach and Richards). The fallacy of using the response of the chemoreceptors to hypoxia in normal individuals to explain the dyspnea of patients is revealed by the marked difference in the behavior of patients and normal subjects to inhalation of oxygen.

The normal individual responds to inhalation of 100 per cent oxygen with a transient increase of pulmonary ventilation of 5 to 7 per cent. However, patients with congestive failure and pulmonary emphysema, in whom an arterial oxygen saturation of 90 to 95 per cent has been found, generally respond to inhalation of oxygen with a decrease in minute volume of respiration of 10 to 30 per cent. Furthermore, continued inhalation of oxygen-enriched atmospheres results in progressive relief of dyspnea despite the previous presence of a normal or nearly normal arterial oxygen saturation. The sensitivity of the chemoreceptors in patients with clinical dyspnea evidently is decidedly different from that of normal human beings. An undue emphasis is at times given to proprioceptive reflexes from the bronchi and lungs, which admittedly play an important role, but by no means as exclusive a one as has been stated by the advocates of the reflex cause of dyspnea, since hypoxia can be demonstrated to be a most significant factor in these cases, i.e., those whose ventilation is decreased by oxygen inhalation. In addition, the arterial oxygen saturations may be found to be normal at times due simply to the effect of the hyperventilation that so often accompanies the drawing of arterial blood in patients, which results in a fictitiously higher saturation than would be present under actual basal conditions.

In our clinic frequent studies have been made on patients with pulmonary emphysema who maintain a burdensome degree of pulmonary ventilation with the result that the arterial blood is almost normally saturated with oxygen. Similarly, patients with congestive failure, in addition to a stagnant hypoxia due to a decreased cardiac output, frequently manifest only a slight lowering of

the arterial oxygen saturation. In both groups the dyspnea is often relieved markedly after one or two days of breathing 50 per cent oxygen, even at a time when the degree of pulmonary congestion is not decreased, as demonstrated by no increase in the vital capacity. Since the reduction in pulmonary ventilation as a result of a test inhalation of 100 per cent oxygen frequently is between 15 and 30 per cent, the hypoxic factor evidently is of considerable importance in the maintenance of dyspnea, and it cannot be minimized, therefore, by a report of a normal or nearly normal arterial oxgyen saturation. Unless it has been shown that oxygen inhalation, comfortably and properly administered, is ineffective in reducing the volume of breathing, the chemoreceptors must be acknowledged to play a more significant role in the dyspnea of pulmonary emphysema than in the respiration of normal people. The increment in pulmonary ventilation due to the effect of hypoxia on these bodies constitutes a large proportion of the maximal breathing capacity of these patients, a circumstance that also ministers to the subjective sensation of dyspnea.

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HYPOXIA DUE TO DEPRESSION OF THE RESPIRATORY CENTER

When an individual has received an overdose of a barbituric acid derivative or other respiratory depressant drugs, the pulmonary ventilation is reduced below normal, and the pressure of oxygen in the arterial blood falls. The respiratory center is depressed, as demonstrated by the failure of these cells to respond to increased concentrations of carbon dioxide. Under these circumstances, reflexes from the chemoreceptors are of manifest importance, since breathing is then stimulated by hypoxia at a time when the respiratory center is depressed by the narcotic. The regulation of respiratory function has changed from the delicate one of carbon dioxide and its resultant effect on pH to the more primitive type produced by lack of oxygen. Under these conditions inhalation of 5 to 10 per cent carbon dioxide does not increase significantly the volume of breathing and is not indicated, since a high CO_2 tension in the blood and respiratory acidosis already are present. Inhalation of 100 per cent oxygen is followed by a sharp fall in respiratory activity and is, therefore, contraindicated, but arterial hypoxia nevertheless must be treated by oxygen in moderate concentrations, adequate to relieve anoxia. If a decrease in pulmonary ventilation takes place of a degree that causes respiratory acidosis, additional means of ventilating the patient should be provided, i.e., by mechanical methods, such as intermittent pressure breathing devices, the tank respirator, or the exsufflator as well as medications which do stimulate respiration, such as benzedrine and caffeine. Intravenous injection of sodium lactate may be employed also to combat respiratory acidosis. In pulmonary emphysema a decrease in pulmonary ventilation of harmful proportions does not generally take place as a result of the properly regulated program of administration of oxygen unless sedative drugs have been used in addition. Even if respiratory depression and acidosis are present, oxygen treatment should not be abandoned but rather continued, with an effective form of artificial respiration as long as is necessary, since damage to brain cells must be prevented, if at all possible, and since the provision of a normal arterial oxygen tension is itself helpful in re-

storing the sensitiveness of the respiratory center to carbon dioxide. In respiratory paralysis due to poliomyelitis, with or without the effect of sedation, an adequate ventilation of the respirator will prevent a CO_2 acidosis, even though supplementary oxygen administration is required.

HYPOXIA IN THE PRESENCE OF A NORMAL TENSION OF OXYGEN IN THE ARTERIAL BLOOD

When tissue hypoxia is present in patients in whom the arterial oxygen saturation is normal, the chemoreceptors of the carotid and aortic bodies are not stimulated, and the pulmonary ventilation is not increased. In cases of carbon monoxide poisoning, in which oxygen want is produced because of the greater affinity of hemoglobin for CO than for O_2, the arterial oxygen saturation of the remaining hemoglobin is normal. The pulmonary ventilation is not elevated, although an increase in cardiac output of approximately 25 per cent has been found with a 50 per cent carbon monoxide hemoglobin concentration. The blood pressure is not raised significantly by hypoxia, but the pulse rate is elevated.

Similarly, in moderately severe anemia the pulmonary ventilation is not significantly elevated, since the arterial oxygen saturation is normal, but Richards and Strauss found the cardiac output elevated. In patients with pulmonary emphysema, inhalation of cigarette smoke has the possibility of aggravating dyspnea because of accumulation of carbon monoxide in the blood; in 18 normal individuals Barach, Eckman, and Molomut found an average arterial CO concentration of 5.7 per cent after inhaling smoke of 20 cigarettes. McFarland found even more serious hypoxic effects from the increase carbon monoxide in the blood.

In patients with congestive heart failure the oxygen pressure in the tissues may be reduced substantially as a result of a stagnant type of hypoxia, but a slight lowering of the arterial oxygen saturation generally is also present as described above.

Another variety of tissue hypoxia in the presence of a normal arterial oxygen saturation is that caused by drugs which exert an adverse effect upon cellular respiratory enzymes, so-called *histotoxic anoxia*, but they rarely are involved in the dyspnea of the patient with pulmonary emphysema, with the exception of alcohol, which is capable of producing histotoxic hypoxia. However, inhalations of high concentrations of oxygen appear to have a favorable effect clinically in the treatment of alcoholic poisoning; that alcohol impairs cardiorespiratory responses to exercise and, futhermore, that oxygen inhalation improves performance of men who have previously ingested alcohol was demonstrated by McFarland and Barach. These results indicate that heavy drinking adds to the hypoxic burden of the emphysematous patient.

ISCHEMIC HYPOXIA

An additional example of hypoxia in the presence of a normal arterial oxygen saturation is that of local tissue oxygen want when the blood supply to an organ is curtailed as the result of embolism, thrombosis, or spasm obliteration of an artery. Local oxygen want in the cells of the brain also results from narcosis with bar-

biturate drugs (Himwich). Other biochemical changes undoubtedly are initiated by hypoxia, such as the diminution in the oxidation of substances important in carbohydrate metabolism of brain tissue, including glucose, lactic acid, and pyruvic acid. The reduction and obliteration of the pulmonary and bronchial arterial vascular supply in the lungs of patients with pulmonary emphysema, especially at the periphery of the chest, is well known.

Inhalation of oxygen-enriched atmospheres is of critical help if some blood supply to the organ involved is still present, not only because of the slight rise in the hemoglobin oxygen saturation but as a result of the sixfold (during the inhalation of 100 per cent oxygen) increase in physically dissolved oxygen delivered to the partially obstructed artery as well as to the collateral vessels. With a 10 per cent increase in oxygen content of each unit of circulating blood, a substantially higher pressure of oxygen is present in the capillaries. Thus, in experimental hemorrhagic shock, inhalation of 100 per cent oxygen resulted in an increase in venous oxygen saturation of from 20 to 33 per cent and an elevation of the partial pressure of oxygen from 14 to 21 mm. Hg.

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The relief of severe coronary insufficiency in cases of coronary thrombosis treated by oxygen is a good illustration of the importance of increase in physically dissolved oxygen (Levy and Barach). That angina pectoris was a syndrome caused by hypoxia of the myocardium was described by Keefer and Resnik, but Boland pointed out that pain in coronary thrombosis and severe angina pectoris was more apt to be relieved by inhalation of 100 per cent than 50 per cent oxygen. Observations of the author indicated that inhalation of 100 per cent oxygen for periods of 20 minutes three times daily results in a reduction in the number and severity of attacks of anginal pain in patients who have many seizures daily. Furthermore, in obliterative arterial disease of the extremities, continuous inhalation of 50 per cent oxygen has been found to relieve pain and to promote healing of gangrenous ulcers. Due to valvular arteritis in rheumatic fever, ischemia of the heart valves has been held responsible for valvular disease itself; inhalation of oxygen during the acute disease was believed responsible for a low incidence of valvular heart disease in patients treated by Poulton. Taran has stated that although oxygen therapy does not reduce measurably the duration of rheumatic activity, cardiac disability is minimized significantly. The use of oxygen in the treatment of cerebral thrombosis was suggested by Poulton, who found in a small series of cases that the end results in oxygen-treated cases appeared to indicate less brain damage than might have been expected. The evidence recited above is strongly suggestive of the value of oxygen treatment of ischemic hypoxia under the circumstances described. The application of these findings to the pathophysiologic disturbance found in the patient with pulmonary emphysema has been mentioned previously and will indeed become clarified in subsequent chapters.

METHODS OF INCREASING RESISTANCE TO HYPOXIA

During World War II, methods of increasing resistance to hypoxia were studied, primarily because of interest in high altitude aviation. Lowering of the total oxygen consumption by thyroidectomy was found to result in a marked

increase in tolerance to hypoxia in experimental animals. This approach, made use of by Blumgart in the treatment of cardiac insufficiency, was tried in cases of pulmonary emphysema. Relief of dyspnea was obtained in some patients; if myxedema is prevented by administration of thyroid extract, the procedure appears to be justified in selected cases.

Of the drugs employed to increase the resistance of the organism to hypoxia, ammonium chloride is a good example of a physiologic alteration of the individual that resulted in a gain in altitude tolerance, i.e., between 2,000 and 2,500 feet. A metabolic acidosis, produced by ingestion of 30 Gm. of enteric-coated ammonium chloride over a period of two days, resulted in an increased ventilation without the hazard of alkalosis, with a fall in alveolar and arterial pCO_2 of approximately 6.5 mm. Hg. At an altitude of 42,000 feet, during an inhalation of 100 per cent oxygen, administration of ammonium chloride produced a net rise in arterial oxygen saturation from 78.7 to 84.8 per cent and in arterial oxygen tension from 41.9 to 53.1 mm. Hg (Barach and associates). The increased pressure of oxygen available to the tissues was due to the more acid blood, which permitted the unloading of oxygen to the cells with a greater head of pressure at a given arterial oxygen saturation, as well as the higher arterial oxygen tension itself. The use of ammonium chloride has not been subjected to special study in cases of pulmonary emphysema, but like Diamox, which also produces an acidosis that results in a lowering of the blood CO_2 tension, it may be beneficial in some cases, due, in our opinion, primarily to its diuretic effect. Both drugs are hazardous as a treatment for acute severe respiratory acidosis since they add a metabolic acidosis.

In a patient with far-advanced pulmonary fibrosis who had been kept alive for seven months by residence in an oxygen room at 50 per cent oxygen, a comatose state developed suddenly when she had been taken out of the chamber on nasal oxygen. Ammonium chloride was given, 18 Gm. in eighteen hours on the day before death, with the thought of displacing the retained blood carbon dioxide. The arterial CO_2 content fell from 132 to 128 and finally to 120 volumes per cent five hours before death. The arterial CO_2 tension was then calculated approximately at 120 mm. Hg (data from Richards and Barach). It would appear that ammonium chloride administration added the harmful effects of a metabolic acidosis. I have since reported the beneficial effects of intravenous injection of sodium lactate, following which the pH promptly rose and the comatose state markedly lessened, with clinical recovery subsequently.

In Fig. 3 the metabolic consequences of ammonium chloride are seen to be a rise in arterial oxygen pressure as consequence of the substitution of oxygen for the displaced CO_2. Under conditions of altitude hypoxia in normal individuals, the benefit from such respiratory stimulation was clearly evident. Furthermore, no impairment of mental function was discerned from the metabolic acidosis produced. In patients with pulmonary emphysema, however, ammonium chloride has been of value was a preparation for administration of mercurial diuretics, but whether any valuable purpose would be accomplished by using it as a method of diminishing CO_2 retention is highly questionable, as will be made more clear in the discussion on Diamox.

Attempts to decrease acute hypoxia at high altitude by conscious hyperventilation did not prove to be of value in our experience, even though the arterial oxygen pressure often can be markedly increased by overbreathing at altitudes of 13,000 to 20,000 feet. However, the parallel decrease in arterial carbon dioxide tension seemed to Eckman and me responsible for failure of improvement in mental functioning. On the other hand, Otis, Fenn, and their collaborators presented good physiologic evidence in support of their belief that optimal tensions of oxygen and carbon dioxide could be produced for various altitudes. The deliberate employment of hyperventilation is, however, of no clinical value to the average conscious patient with pulmonary emphysema for reasons to be discussed later, and it is not possible of achievement in the presence of respiratory acidosis and semicomatose states.

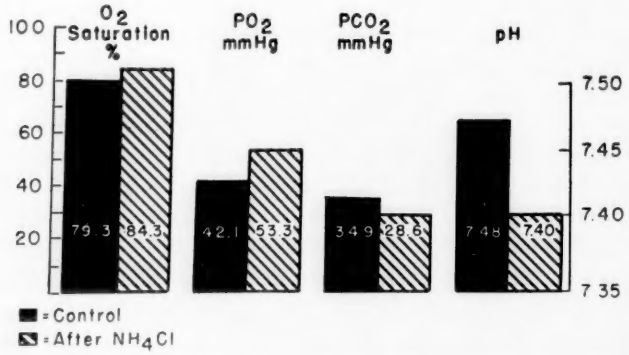

Fig. 3—Rise in arterial pO_2 and fall in pCO_2 following ingestion of ammonium chloride in healthy subjects produced by ventilatory stimulus of a metabolic acidosis.

The inhalation of carbon dioxide does diminish hypoxia at moderate altitudes because the increased pulmonary ventilation raises the alveolar oxygen percentage, but it is more practical as well as more comfortable to inhale oxygen-enriched atmospheres. Carbon dioxide therapy has no value to the patient with pulmonary emphysema, even for the production of cough and expectoration, since diffusion of CO_2 is manifestly impaired in these cases. In addition, the abnormally small ventilatory response to CO_2 inhalation characteristic of these cases is not reversible (Fishman, Samet, and Cournand).

The effect of diet on resistance to hypoxia at altitude has been studied over a long period of time. A high carbohydrate diet results in an increased R.Q.; a higher production of carbon dioxide with a given oxygen consumption produces a proportionate rise in alveolar ventilation and, therefore, in arterial oxygen tension. At high altitudes, where 100 per cent oxygen is breathed, differences in the metabolic R.Q. would not affect the alveolar R.Q. which always remains at unity, and, therefore, no benefit could be expected under these circumstances. At altitudes such as at 15,000 feet, where air is breathed, the comparison between results of a high carbohydrate meal and a high fat-protein meal showed that an

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increase in ceiling altitude of 1,000 to 2,000 feet took place. However, in cases of pulmonary emphysema, an increased CO_2 production does not result in an increased volume of breathing, and diet plays no special role in this entity.

DECREASE OF ALTITUDE HYPOXIA BY BREATHING OXYGEN UNDER POSITIVE PRESSURE

The inhalation of oxygen under continuous positive pressure by a mask was introduced clinically in 1935 for the treatment of left-sided heart failure by Poulton in England and for the treatment of acute pulmonary edema and obstructive dyspnea in this country by Barach and associates. Pressures between 4 and 13 cm. of water were used therapeutically for these disturbances in respiratory function. The reason for employing pressure breathing at high altitudes was to increase the arterial oxygen pressure and thereby effect a gain in altitude tolerance (Gagge and associates). Since the purpose of pressure breathing was to increase the efficiency of performance at any specified high altitude, the degree of pressure that could be tolerated and the effects of these pressures were studied extensively during the war. When oxygen was breathed under an added pressure applied continuously throughout the respiratory cycle, it was called continuous positive pressure breathing (C.P.P.B.). Intermittent positive pressure breathing (I.P.P.B.) is the procedure in which the mask pressure is considerably higher at inspiration than at expiration. The effect of the added ventilatory pressure on the circulation, venous pressure rise, and cardiac output was found to be equivalent to the mean increase in pulmonary pressure; the alveolar oxygen pressure was additionally elevated by the induced hyperventilation.

When oxygen is inhaled by a mask under continuous positive pressure, the added mask pressure results in an increase in arterial oxygen pressure equal to that which would have been obtained if the barometric pressure itself had been raised correspondingly. If the breathing pattern is unchanged, and the alveolar CO_2 is constant with pressure breathing, then the added mask pressure is added to the alveolar oxygen pressure. If air were inhaled, then the increase in alveolar oxygen pressure would be only one-fifth of the added mask pressure, since air contains 20.9 per cent oxygen. This procedure was therefore of value at altitudes higher than 34,000 feet, at which the inhalation of 100 per cent oxygen compensated for this degree of altitude anoxia. At an altitude of 42,400 feet, the arterial oxygen found, when subjects breathed pure oxygen at 15 mm. Hg mask pressure, was the same as that present at an altitude of 40,000 feet when pure oxygen was breathed without pressure. A gain of 2,400 feet in altitude was thus produced by this procedure; this accomplished an increase of from 80 to 89 per cent in arterial oxygen saturation (Gagge, Barach, Fenn, Helmholtz, and others).

The use of a pressure as high as 15 mm. Hg, however, was attended by a decreased cardiac output in the majority of normal individuals of the order of 20 to 25 per cent lower than control values as determined by both the ballistocardiograph and the Fick method. The vertical diameter of the heart was increased. The electrocardiogram showed characteristic changes due to the rotation of the heart with notably a depression of the T wave. In normal individuals, about 40 to 50 per cent of pressure applied at the mask was found to

be absorbed by the elasticity of the pulmonary parenchyma and the bronchi, the remainder being passed on to the intrapleural space and the outside of the heart. The venous pressure was elevated approximately 40 to 50 per cent, which maintained a return of blood to the right side of the heart at a higher level of intra-auricular pressure. The systolic blood pressure rose almost as much as the applied mask pressure so long as the cardiac output remained constant.

With intermittent pressure breathing, the highest pressure was during inspiration and the lowest pressure varied from zero to one-third the inspiratory pressure. The increase in the arterial oxygen pressure was achieved in part by the mean average pressure and in part from the hyperventilation induced by intermittent pressure breathing, since some alveolar CO_2 was replaced by oxygen. However, the gain in arterial oxygen pressure as a result of a loss of CO_2 did not in our own studies represent an increase in efficiency of the subject because excessive hyperventilation produced alkalosis and, at times, tetany. Even in the absence of tetany the performance of individuals tested with intermittent pressure breathing did not always correspond to the gain in arterial oxygen pressure achieved by a loss in carbon dioxide. Furthermore, in respect to the increase in altitude attained by pressure breathing, continuous P.B. was more comfortable than an equivalent mean pressure derived from intermittent pressure breathing. The modern devices for I.P.P.B. have been found effective for the treatment of pulmonary edema and respiratory acidosis.

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Although an individual with a tendency to underventilate would be benefited by a certain degree of hyperventilation, a valuable exchange of more acapnea for less anoxia was difficult to acheive, expecially when consideration is given to the significant diminution in cerebral blood flow that accompanies passive hyperventilation of moderate degree. Although theoretical evidence, as mentioned above, supports the use of moderate hyperventilation to overcome altitude hypoxia (Fenn, Otis, and others), its use at barometric pressure near sea level, either voluntarily or by mechanical means, is fraught with the hazards of the hyperventilation syndrome in both normal and dyspneic subjects.

Hyperventilation of moderate intensity was found by Schmidt and his associates to be accompanied by a decrease in cerebral blood flow of 30 per cent, with a reduction of cardiac output of approximately 11 per cent. It is of interest in this connection to point out that about 20 per cent of the total cardiac output and 24 per cent of the total oxygen consumption are devoted to the brain, which is only 2 per cent of the body weight. The effect of marked hyperventilation at sea level is to decrease approximately 40 per cent the arterial oxygen pressure, to which the brain cells are exposed. Carryer has stressed the importance the respiratory alkalosis produced by hyperventilation, manifested clinically by anxiety, giddiness, and confusion. A reduction of the carbon dioxide in the serum from 45 to 15 mm. Hg brought about an alkalotic state which, according to his calculations, reduced by 60 per cent the amount of oxygen released in the tissues. The symptoms and signs of hypoxia may also be produced in the emphysematous patient with normal pH by immoderate hyperventilation.

THE ACCLIMATIZATION RESPONSE TO PROLONGED HYPOXIA

The acclimatization response to high altitudes, such as 22,000 feet, has been recently studied by Houston and Riley through the use of low pressure chambers in which men were exposed to a gradual decrease in barometric pressure produced over a period of 30 days. Although there was an average 37 per cent increase in hemoglobin, as measured by the oxygen capacity, an additional major compensatory reponse appeared to be an increased pulmonary ventilation, which to a degree increased the arterial oxygen pressure, lowered the pCO_2 and, secondarily, the blood bicarbonate. Although the arterial pH shifted to the alkaline side, the production of an injurious alkalosis was prevented by the buffering action initiated by loss of bicarbonate through the kidneys. The oxygen consumption of the subjects did not change and, although the tissues were exposed to a considerable degree of hypoxia and cellular function presumably impaired, the subjects themselves felt well and considered themselves in good condition. With an increase in cardiac output the decreased AV difference raised the venous pO_2, thereby increasing the mean capillary pO_2 and aiding the delivery of oxygen to the tissues. A marked reduction in pO_2 gradient occurred between arterial and mean capillary blood, a reduction due primarily to the inherent characteristics of hemoglobin.

A study* of the response of a patient with advanced metastatic cancer to similar gradually decreasing oxygen concentrations revealed interesting comparative data. The patient was acclimatized to 10 per cent oxygen, equivalent to an altitude of approximately 18,000 feet, during a period of 35 days. Although the oxygen saturation and tension of arterial blood fell to a level comparable to the average values of the subjects studied by Houston and Riley at a comparable altitude, the pH of the blood shifted to the acid side rather than toward alkalinity. This metabolic acidosis appeared to be the result of severe impairment of the function of the liver, due to the presence of large metastases, as well as, presumably, the effect of hypoxia on an already damaged organ. The patient was not short of breath during the period of residence in the low oxygen atmosphere, except during walking. The volume of the pulse, which was markedly diminished during the last two days at an oxygen concentration of 10 per cent improved on return of the patient to atmospheric pressure. It was noteworthy that the red count was unchanged at 3.9 million although in normals tested at similar degrees of hypoxia a rise in red blood corpuscles from 4.5 to about 6 million, depending on the length of exposure to altitude, takes place.

In reviewing the respiratory features of acclimatization to altitude, Riley, Otis, and Houston point out that the low oxygen pressure and the high pH found during exposure to altitudes between 18,000 and 22,000 feet have deleterious effects upon cellular function, that the ventilatory changes are such as to suggest that a balance is struck between the evils of hypoxia and hypocapnia, and that acclimatization to altitude is a matter of adjustment to a low pCO_2 as well as to a low pO_2. During the period of adaptation the whole blood buffer base is reduced by selective excretion of fixed base and retention of fixed acid by

*Barach, A. L., Holaday, D., Graff, S., Beck, G., and Bickerman, H. A.: Physiological Effect of Acclimatization to Hypoxia in a Patient With Advanced Metastatic Cancer. To be published.

the kidneys. This process, in the terminology of Singer and Hastings, leads to metabolic acidosis which is secondary to the respiratory alkalosis. The pH of the blood which may be elevated to the vicinity of 7.6 is restored toward normal as a result of continued base excretion provided the acclimatization process is successfully carried out for a sufficient time. As a result of the loss of base a further increase of ventilation and lowering of pCO_2 becomes possible without excessive elevation of pH. An important consequence of the increase in ventilation and lowering of pCO_2 is naturally the accompanying elevation of alveolar pO_2.

However, when the subject returns quickly to sea level, his ventilation continues at the high rate and returns to normal very gradually over a period of days or perhaps weeks. The explanation of this appears to be the acid base mechanism which stimulates ventilation sufficiently to prevent the pH of arterial blood from falling much below 7.40. Because the acclimatized subject has at this time a low buffer concentration in the blood, the arterial pCO_2 must be kept correspondingly low to prevent respiratory acidosis, i.e., by maintenance of a high pulmonary ventilation. When the buffer base is increased the ventilation decreases. If these considerations are kept in mind in reference to mechanical hyperventilation of the pulmonary emphysema, it will be seen that continued loss of pCO_2 must be followed by a loss in buffer base, with the result that the patient has the burden of eliminating carbon dioxide produced in the body by a degree of augmented ventilation that may indeed result in dyspnea, because of the restricted nature of the pulmonary bellows. Unless the diffusion capacity of his lungs had been notably improved by other measures, acidosis would appear to be more likely to take place on activities resulting in increased CO_2 production.

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Although Fishman, Samet, and Cournand believe that elimination of carbon dioxide, as accomplished by Diamox therapy, may restore mental alertness and a sense of well-being and diminish the threat of CO_2 narcosis, our opinion is that this sequence of events is not apt to take place in patients who have developed the homeostatic mechanism of eliminating CO_2 at a higher pCO_2 tension without acidosis. It is true that the metabolic acidosis produced in healthy by ammonium chloride, did not result in the irrationality that is initiated when a CO_2 acidosis takes place. However, in the many patients whom we have observed, oxygen treatment was followed by a gradual rise in arterial CO_2 content to a range between 80 and 100 volumes per cent with a maintenance of normal pH and an alert mental state. The increased CO_2 concentration in the alveolar air which results in a greater elimination of carbon dioxide per unit of ventilation is not a completely successful mechanism, but it does appear to permit the decreased breathing engineered by the effect of oxygen in the carotid sinus to take place without the development of an undue fall in pH and with relief of shortness of breath. This adaptive mechanism, which will be discussed again in the section on oxygen therapy, is illustrated schematically in Fig. 4 in which it will be seen that the same quantity of CO_2 may be eliminated with a decreased tidal air if the expired CO_2 is proportionately elevated.

A slight increase in the requirements for gas exchange in the lung which results in a moderate increase in pulmonary ventilation may nevertheless initiate severe dyspnea in patients who have mechanical difficulty in breathing. The

work of breathing, which is to some extent dependent on the volume of breathing, is lessened by inhalation of oxygen both at rest and during exercise. The mechanism of adaptation of the patient with pulmonary emphysema is then seen to be in some respects opposite to that of the normal man adapting himself to altitude hypoxia, namely, an increase in the elimination of chlorides and retention of base with the result that the pH of the blood remains stationary when exposed to a graded acclimatization to increasing oxygen concentrations in the atmosphere.

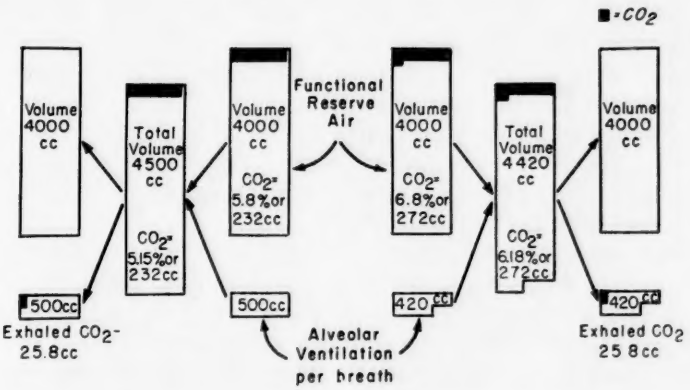

Fig. 4—The chart illustrates schematically the adaptive mechanism whereby the same quantity of CO_2, 25.8 c.c., is eliminated per breath with a decreased tidal air (and pulmonary ventilation) when the expired CO_2 increases from 5.8 to 6.8 per cent.

In our view this is made possible only by the elimination of carbon dioxide at high partial pressures in the arterial blood. As indicated elsewhere, an improvement in diffusion of oxygen and carbon dioxide gases within the lung is preferably achieved by suitable physiologic, antibiotic, and hormonal therapy. Although sufficient evidence may be forthcoming to challenge this opinion, I have not at the present writing encountered studies which justify the attempt to reduce the CO_2 tension of arterial blood by either Diamox or mechanical ventilation in patients with a normal pH.

In some patients with pulmonary emphysema, especially those with right heart failure, polycythemia is present. In other cases the hemoglobin may remain down despite the presence of long-continued arterial hypoxia. The factors which prevent a compensatory rise in red blood corpuscles under these circumstances have not been elucidated.

Increasing hypoxia takes place without oxygen therapy in some cases of pulmonary emphysema as a result of impairment of diffusion and ventilation, accompanied by an acidosis due in the main to CO_2 retention. However, in patients with heart failure, congestion of the liver and kidneys, an additional factor which may contribute to the marked fall on pH may be the effect of incomplete oxidation of the products of metabolism, a reaction similar to the metabolic acidosis produced by inhalation of low oxygen atmospheres in the patient described above, despite a moderate hyperventilation response to hypoxia.

That proprioceptive reflexes play a role in augmenting dyspnea in respiratory illness characterized by increased pulmonary ventilation undoubtedly is true, but their importance seems to me to have been overemphasized both in passive pulmonary congestion and pulmonary emphysema in comparison to chemical factors, i.e., the arterial oxygen and carbon dioxide tensions and pH.

REFLEX AND CHEMICAL CONTROL OF RESPIRATION

The sensory receptors in the smooth muscle spindles in the walls of the bronchioles throughout the lungs are stimulated mechanically by inflation of the lungs and stretching of the muscles; transmission of these impulses to the respiratory centers takes place through the vagus nerve. Investigations of the effects of stimulation of the vagus nerve in the rabbit support the concept of a reciprocal innervation between the inspiratory and the expiratory centers, which is opposed to the concept of two sets of receptors and afferent fibers to the respiratory center in this nerve (Wyss).

Repeated attempts indeed have been made to strike a fair balance between factors involved in the production of an increased volume of breathing in muscular exercise and in dyspnea in clinical illness. The original observations of Haldane showed clearly that carbon dioxide is a powerful respiratory stimulant and that the respiratory center in the healthy individual is very sensitive to changes in alveolar or arterial carbon dioxide tension. Winterstein and Hasselbach proposed that the arterial pH rather than the pCO_2 was the effective regulator of respiration. The original theory of Haldane was modified additionally by Gesell, who emphasized that alterations in respiratory activity were governed by the pH or acidity of the cells of the respiratory center. Evidence for and against the hypothesis that carbon dioxide was the most important stimulus to the medullary center, independent of its effect on the acid base equilibrium of the blood, has been reviewed by Bernthal, Schmidt, and Comroe.

Since the studies in 1913 of Krogh and Lindhard on muscular exercise, the reflex origin of dyspnea has been emphasized by may investigators, including Peabody and Wentworth, and Cullen and associates, in cases of heart disease with dyspnea, and by Knipping and associates, Cournand and associates, Baldwin and associates in pulmonary emphysema and fibrosis.

Hess and Fleisch considered that the respiratory center determined the volume of breathing, and physical or proprioceptive reflex impulses from various parts of the breathing apparatus, the manner or form of the ventilation. In evaluating the importance of humoral factors, the influence of hypoxia on the chemoreceptors is considered a reflex of chemical nature, even though hypoxia itself under ordinary circumstances does not have a direct effect upon the respiratory center. Recently, Sarnoff and associates have shown that inhibition of spontaneous respiration can be produced by stimulation of one or both phrenic nerves in such a way as to obtain an effective diaphragmatic contraction and relaxation. This inhibition of spontaneous breathing was said to be both of reflex and of chemical origin. The reflex factor was demonstrated by a section of the vagus nerve, but it was shown also that spontaneous respiration could be inhibited by overventilation induced electrophrenically. Despite the attempt

to analyze the components in clinical dyspnea, such as in pulmonary emphysema and pulmonary fibrosis, it is difficult to separate the effect of chemical stimuli from those originating in the proprioceptive sense organs of the lungs and the chest wall by the functional tests now in use. To regard the chemical factor as relatively unimportant in the dyspnea associated with passive pulmonary congestion in heart disease or in pulmonary emphysema on the basis of a normal or nearly normal oxygen saturation is to commit an error based on the absence of complete clinical data, since, as we mentioned previously, inhalation of oxygen results generally in a significant reduction in the volume of breathing and in relief of dyspnea. The mechanism which is only partially beneficial will be discussed again in connection with therapeutic administration of oxygen.

An interesting example of the priority of the chemical stimulus to respiration over proprioceptive reflexes is revealed in the mechanism of the equalizing pressure chamber in which lung ventilation takes place without lung movement. In 1926 Thunberg placed patients with respiratory paralysis in a chamber in which an alternating pressure of one-seventh of an atmosphere was produced 25 times a minute. This resulted in an increase and decrease of density of the air within the chamber equivalent to a tidal volume in the human subject of 400 c.c. The mechanism of this type of pressure respiration was based on Boyle's law, i.e., the number of gas molecules in a container varies with the degree of pressure when the temperature is constant. Barach investigated the effectiveness of this method of artificial respiration in experimental respiratory paralysis in animals and found it inadequate to maintain normal respiratory function; the arterial oxygen concentration gradually fell with an accompanying carbon dioxide retention. It appeared from these studies and from subsequent observations on patients exposed to alternating pressure that the chest was compressed initially by the positive pressure wave to an extent slightly greater than the subsequent expansion produced by negative pressure. Since the resistance of the tracheo bronchial tree was responsible for unequal pressures being exerted on the inner and outer surfaces of the thorax, a chamber was constructed in which air first entered the head end of the chamber and then the body compartment, a constriction interposed by a movable partition around the neck being responsible for accurate counterbalancing of the resistance in the respiratory passageway.

The result of the method of "equalizing alternating pressure" was that there was no inequality between the initial positive and negative pressures outside and inside the lungs. When animals were subject to respiratory paralysis and then treated with this technique, the arterial oxygen and carbon dioxide tensions were maintained in a normal range. Furthermore, both normal individuals and patients with chronic pulmonary tuberculosis were able to reside in the chamber, with complete absence of chest movement, cessation of the impulse to breathe, and with a constant lung volume, although a normal pulmonary ventilation was being provided in the equalizing pressure chamber. The chemical and physical factors that stimulate respiration were abolished by (1) a satisfactory gas exchange and (2) the maintenance of an intra pulmonary pressure equal to that of the chest wall and the diaphragm. When patients with pulmonary emphysema were placed in the alternating pressure chamber, relief of dyspnea was immediate, the con-

sequence of improved gas exchange due to the provision of an increased ventilation and diffusion of gases from the lungs into the arterial blood. Chest motion was not abolished because of inability to compensate for the high bronchiolar resistance.

PHYSIOLOGIC THERAPY IN PULMONARY EMPHYSEMA

In selecting the term of "physiologic therapy of respiratory disease," my intention was to emphasize a form of treatment that was largely an outgrowth of studies on the pathologic physiology of bronchopulmonary illness; its basic purpose may be defined as an attempt to correct deviations from the normal functioning of the lungs and to eliminate, whenever possible, reversible pathology in these organs. Clinical disorders of breathing have especially lent themselves to measures of this kind, i.e., that improved physiologic behavior of the respiratory system.

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The therapeutic use of gases began with the administration of oxygen which, when Priestley discovered it, was the occasion of his engaging comment, "I reduced a large jar full of it to the standard of air but I fancied that my breath felt peculiarly light and easy for some time afterwards. Who can tell but that in time this pure air may become a fashionable article in luxury. Hitherto, only two mice and myself have had the privilege of breathing it." Shortly after Lavoisier proved that oxygen was the substance necessary for life, Thomas Beddoes in 1800 established a pneumatic institute at which oxygen therapy began with the treatment of heart disease and asthma by inhalation of oxygen. It is probable that treatment of the bronchospastic type of pulmonary emphysema began at this time.

The use of carbon dioxide as a therapeutic gas, which began with the purpose of stimulating the breathing in cases of respiratory depression, has now been largely abandoned, since, in the various clinical entities in which it occurred, a respiratory acidosis was already existent. The administration of CO_2 is employed in the treatment of hiccough, to produce states of unconsciousness in the therapy of mental disease, and, in a few clinics, to stimulate the breathing in postoperative patients. Inhalations of carbon dioxide have been advocated to promote expectoration in chronic bronchitis, emphysema, and associated clinical entities, but the results of its use were not sufficiently clear-cut, in contrast to other more effective procedures, to result in its adoption by most clinics.

USE OF HELIUM

The introduction of helium as a therapeutic gas was based on its lowered specific gravity in relation to nitrogen or oxygen, being one-eighth as heavy as oxygen, since the velocity of movement of a gas through a constricted orifice is inversely proportional to the square root of the molecular weight of the gas. If the constriction were continued in a linear direction, Poiseuille's law would then become applicable and, to the extent that viscosity itself became an influence, there would be no advantage in substituting helium for nitrogen, since the latter is slightly less viscous. I advocated the use of 80 per cent helium with 20 per cent

oxygen to decrease the physical effort of breathing in obstructive dyspnea; the physical principle of effusion and diffusion are involved in the benefit obtained. Under conditions of experimentally induced tracheal obstruction the substitution of inhalation of a helium-oxygen mixture for air was followed by a decrease in the pathologically elevated inspiratory negative intrapleural pressure. It was, indeed, in localized laryngeal constriction that inhalation of this lighter-than-air gas most conspicuously relieved dyspnea. Dean and Vischer explained the physical advantage of helium in decreasing the work performed under these circumstances as due to its lower turbulent resistance in comparison to nitrogen. The first patient treated with inhalation of this helium-oxygen mixture fell fast asleep within one minute. The immediate physical and mental relaxation achieved by the decrease in the physical effort of breathing resulted subsequently in a diminution in bronchospasm itself.

The physics of air movement under conditions of localized obstruction in the respiratory passageway may be readily reproduced when a normal individual is allowed to breathe air through a 1/8 inch orifice. The sensation of dyspnea begins immediately and is not at all diminished by breathing 100 per cent oxygen. However, when a mixture of 10 per cent oxygen and 90 per cent helium is substituted, the difficulty of breathing is immediately relieved since the mechanical effort necessary to pull this very light gas is sharply reduced. A moderate degree of relief is invariably experienced during inhalation of 20 per cent oxygen with 80 per cent helium; with the addition of continuous pressure breathing of 5 to 10 cm., or with intermittent pressure breathing, the sensation of dyspnea is almost completely relieved. The conventional gauge on the oxygen tank used on the helium-oxygen cylinder at a dial setting of 1 liter of oxygen, results in a flow of 1.7 liters per minute of the 80 per cent helium, 20 per cent oxygen mixture. Thus when the oxygen regulator is set at 10 liters, 17 liters of the helium-oxygen gas will enter the collecting bag. Conversely, it was demonstrated that the pressure required to move a constant volume of the helium-oxygen mixture was less in proportion to that required to deliver oxygen, namely, in the proportion of 1 to 1.7, i.e, not quite half the physical force is required to move a helium-oxygen mixture than oxygen.

Nevertheless, in clinical conditions in which constriction of any part of the respiratory passageway results in areas of turbulence, often as a result of the augmented ventilation in the dyspnea of bronchial asthma, pulmonary emphysema and tracheo bronchial constriction, inhalation of helium-oxygen mixture has the beneficial effects described due to the fact of the decreased density of the mixture, i.e., one-third that of air.

Since Schiller and co-workers reported that the use of helium was of no value in bronchial asthma, even though the minute volume was admittedly increased in the majority of their cases during its inhalation, reference will be made to other investigations which clearly indicate its functional advantages as well as its therapeutic efficacy. Maytum, Prickman, and Boothby confirmed the principles involved by stating that it both decreased mechanical work and aided diffusion. Their clinical results in three cases of status asthmaticus were described as follows:

The condition of the patient in all three instances was alarming. In each case extreme dyspnea was present and very little air was entering the lungs. Cyanosis was marked and was not relieved by administration of oxygen with concentration greater than 80 per cent, and the usual treatment had no effect on the symptoms. Although death from asthma is uncommon, all three of these patients appeared to have reached the point where death might ensue if relief were not obtained soon.

When a mixture of helium and oxygen was substituted for air and oxygen in the oxygen tent, the condition of all three patients almost immediately improved, both subjectively and objectively. Respiration was less difficult, cyanosis disappeared rapidly, and the patients were able to relax and to obtain much needed rest.

Studies by Otis, Fenn, and Rahn revealed that the maxium rate of breathing at sea level, 30 breaths and 150 liters per minute, indicated that the total work was 9 Kg. per breath, whereas, at a barometric pressure of 226 mm. Hg the work of breathing was 4.3. The work due to streamline flow was 2.2 in each instance but the reduction in turbulent work was from 6.8 to 2.1 as a result of the diminished density of the air. Since turbulence varies with the square of the velocity and its constant K is inversely proportional to the density of the air, similar results may be produced by inhalation of helium-oxygen mixtures having a comparable density. In fact, in one of our patients with Cheyne-Stokes' dyspnea reported in 1935, the spirometric record indicated a marked increase in tidal volume, from 605 to 794 c.c., as well as a long pause between periods of rapid respiration due to the increased washing out of carbon dioxide with 80 per cent helium and 20 per cent oxygen as contrasted to the record obtained with the patient breathing air. The period of apnea when breathing air was 2.0 seconds, when breathing the helium oxygen mixture 12.4 seconds. The sensation of air hunger was notably diminished. Other tracings revealed the effect of helium on the mechanics of breathing in bronchial asthma and pulmonary emphysema, with and without added intrapulmonary pressure (1934-1938)

In a study of the author with Eckman, a motor was employed to raise and lower a weight to a spirometer bell at a constant number of revolutions per minute. The inlet of the spirometer was constricted to between 0.31 and 0.75 inch. Comparisons were made between the extent of filling of the spirometer bell and the pressure within the system when the apparatus breathed air and helium oxygen mixtures. With the use of the latter light gas the increase in tidal air varied between 2 and 21 per cent. When oxygen alone was employed there, the contrast was even more evident due to increased molecular weight of oxygen. A brief experiment with hydrogen gave slightly better results than with helium.

Maytum, commenting on the good results obtained in four cases of intractable asthma with the clinical use of the helium-oxygen mixture, reported by Prickman, Boothby, and himself, observed subsequently concerning inhalation of helium with oxygen, "I consider it to be the most valuable treatment at present for status asthmaticus and to be of definite value in the treatment of other obstructive lesions of the respiratory track. . . . It is of the greatest value in cases of transient obstruction and if the lesion is in the larynx, tracheotomy may be avioded in some cases. This is particularly true in cases of postoperative of traumatic edema of the larynx and of transient paralysis of the cord occasionally seen after thyroidectomy."

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Eversole studied the use of helium-oxygen mixture in cases of partial obstruction of the larynx or trachea and reported that of 105 cases, 55 obtained complete relief, 37 partial relief, and 13 no relief from inhalation of helium-oxygen therapy. The number of studies confirming the value of inhalation of helium with oxygen when properly administered in patients with intractable asthma and obstructive dyspnea, including those of Segal, Kernan, Bickerman, Beck and others, have made it clear that the physical work of breathing was diminished and that diffusion of gases in the helium atmosphere was increased.

In pulmonary emphysema, bronchial constriction is less localized; however, as a consequence of its higher diffusion capacity, inhalations of helium and oxygen may penetrate alveoli that may be relatively impermeable to air or oxygen. Furthermore, an advantage necessarily takes place when obstruction to flow is due to turbulent resistance which, as shown elsewhere, is increased in cases of pulmonary emphysema with an augmented ventilation. A sensation of relief is generally noticed by these patients during inhalation of 80 per cent helium and 20 per cent oxygen. Since hypoxia is so frequently present in this disease, 25 to 30 per cent oxygen with the remainder helium has been employed at times for 15 to 20 minutes three times daily. The administration of these mixtures is generally carried out with the Meter mask in order to aviod rebreathing of carbon dioxide, often with the expiratory pressure attachment set at 4 cm. H_2O. Mixtures of 25 to 30 per cent oxygen and 75 to 70 per cent helium are also employed in intermittent pressure and continuous breathing devices to accomplish more efficient aeration of the alveoli and to reduce the respiratory effort. The routine administration of helium-oxygen mixtures in cases of bronchial asthma and pulmonary emphysema has declined in recent years. The increasing use of corticosteroids, especially prednisone, combined with continuous nebulization of bronchodilator aerosols, have rendered the problem of bronchospasm more amenable to treatment. There are, nevertheless, instances of severe dyspnea in which combination of helium with oxygen combined with pressure breathing serve a useful purpose; the decreased ventilation that often follows the use of these procedures is associated with a more efficient diffusion of oxygen and carbon dioxide. In Fig. 5 the effect of inhalation of 20 per cent oxygen and 80 per cent helium under a continuous pressure of 4 cm. H_2O is seen to produce a decrease in the volume of breathing from 8,560 to 6,940 c.c. per minute accompanied by a diminution in the length of the expiratory cycle. This patient appeared to have a type of obstructive dyspnea associated with bronchitis obliterans in addition to pulmonary emphysema and fiberosis.

OXYGEN THERAPY IN PULMONARY EMPHYSEMA

Inhalation of oxygen is instituted in many cases of pulmonary emphysema when an acute exacerbation of the disease takes place, manifested by severe dyspnea, cyanosis, tachycardia, and, at times, mental confusion. Arterial hypoxia and CO_2 retention are increased and, in some cases, accompanied by an acid shift in pH. Abrupt impairment of respiratory function takes place most commonly as a result of infection, either viral in nature due to the common cold or atypical pneumonitis, or as a result of pyogenic bronchopulmonary disease.

Other pathophysiologic events that result in a worsening of the emphysematous state include intractable bronchospasm as a result of exposure to allergic agents or refractoriness to bronchodilator drugs, alveolar over distention following undue severe physical exercise, and failure of the right or left heart.

The determination of the peripheral venous pressure is naturally helpful in estimating the degree of insufficiency of the right ventricle, along with other evidences of cor pulmonale, as will be discussed by Richards and Fishman.

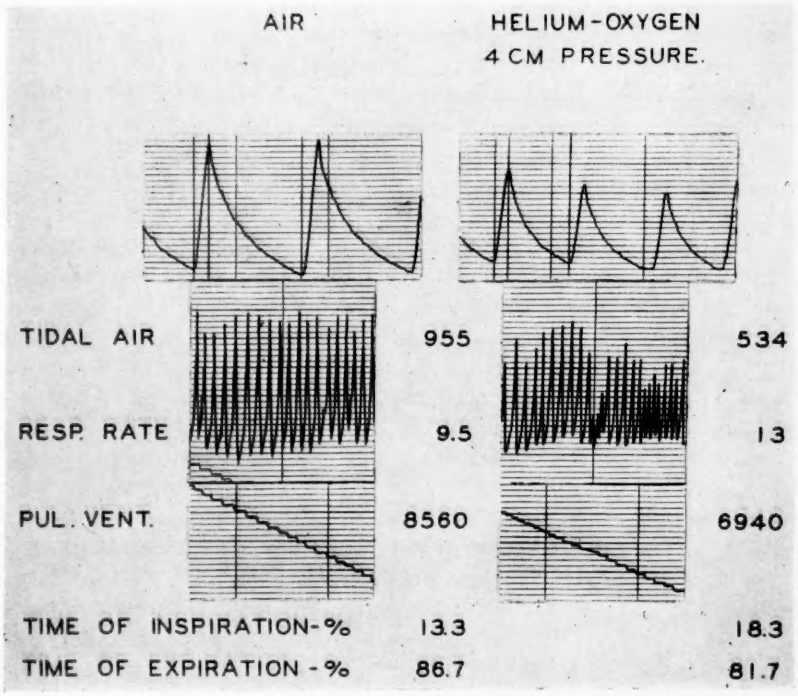

Fig. 5.—Spirometric records in a patient with pulmonary emphysema, pulmonary fibrosis, and chronic bronchitis reveal the unusually long duration of expiration spontaneously adopted by the patient. The diminution of dyspnea produced by inhalation of 80 per cent helium with 20 per cent oxygen under continuous pressure of 4 cm. H_2O was manifested by a decrease in pulmonary ventilation from 8,560 to 6,940 c.c. per minute and in tidal air from 955 to 534 c.c., as well as a diminution in the previously excessively prolonged expiration. (From Barach, A. L.: Am. J. Surg. 89:376, 1955).

Failure of the left ventricle is far more difficult to detect since the breath sounds are diminished and moist râles are infrequently audible. In either event, the administration of oxygen is a specific measure for rapid correction of the circulatory disturbance induced by hypoxia; it is also more effective than other forms of cardiac therapy, as shown by Dexter and associates, who reported that the cardiac output was restored toward the normal when it was elevated, as in cases of pulmonary emphysema and cor pulmonale with increase in total pulmonary resistance, and also when it was lowered, as a result of the added load of poor oxygenation on an already overworked heart muscle.

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The indication for treatment is the continuous, not intermittent, inhalation of oxygen in such a manner as to relieve hypoxia without the development of unfavorable reactions. Abrupt exposure to an atmosphere of 40 to 50 per cent oxygen is rarely necessary to save life, since substantial relief of oxygen want may be provided by the inhalation of 25 to 30 per cent oxygen. The most practical method of obtaining the objective of a graded increase in oxygen concentration consists in the use of the rubber catheter inserted in the nasal pharynx or, if desired, into the oropharynx. This should be removed regularly at six-hour intervals and lubricated with K-Y jelly. After several days, when the patient is in better control of his physical and mental faculties, a double bent nasal catheter or plastic tube, which is inserted ½ inch within the nares, is substituted since it is far more comfortable and provides an adequate concentration of oxygen in the inspired air with suitable flows.

The program or oxygen administration originally outlined in 1938, consists of a flow of 1 or 2 liters per minute for the first 24 hours, with an increase of 1 liter per minute every day or, in the event of increasing drowsiness, every other day until a flow of 7 liters per minute is attained. This will generally result in a concentration of approximately 38 per cent in the inspired air, varying somewhat with the degree of hyperventilation. At this time, if desired, an oxygen tent may be substituted with a concentration of 40 per cent oxygen, maintained with a flow of 10 to 12 liters per minute and sufficient leakage to insure that the atmosphere does not contain more than 40 per cent oxygen by test. If cardiorespiratory compensation appears to be substantially restored at the end of one to two weeks' additional treatment, the double nasal tubes are reinserted with an oxygen flow of 7 liters per minute; a gradual decrease in the administration of oxygen takes place by lowering the flow 1 liter per minute every day or every other day until the patient is returned to an air atmosphere. This method is to be preferred to the employment of oxygen intermittently. The latter procedure is fraught with the hazard of sudden changes of oxygen tension which leads to the patient becoming addicted to oxygen. The consequence of employing intermittent oxygen therapy is not simply the abrupt precipitation of dyspnea when a mask or a tent is removed as the effect on mental function, manifested in most cases by the patient feeling dizzy, restless, and anxious, long before shortness of breath takes place. With the method of gradually decreasing the oxygen concentration, compensations develop, including an increase in hemoglobin and red blood count, elevated pulmonary ventilation and decrease in blood bicarbonate.

This program is not apt to be followed by respiratory acidosis and coma if sedatives are withheld. Morphine is lethal and barbiturates undesirable. Paraldehyde is preferred by Simpson, who, having observed the comatose state as a result of the administration of high concentration of oxygen, recently stated:

> . . . I have, more recently, used this method in severely ill and disoriented patients and have avoided coma, which, I feel sure, would have supervened had they been put at once into an oxygen tent. I therefore now use Barach's method in every case except those in which urgency demands the use of an oxygen tent. Coma in the tent is by no means necessarily fatal. Even if the patient dies in the tent, it must be remembered that the severity of the infection, the duration and degree of the anoxia, and the cardiac status all have important bearing on the immediate prognosis . . . . Ex-

cept when a patient's critical situation demands a tent, oxygen is now given initially by nasal catheter and the flow rate is gradually increased to aviod coma. Respirators have been of little use with comatose patients since the rhythm of their depressed but functioning respiratory center cannot be paralleled by the machine.

The measures employed in the treatment of respiratory acidosis, discussed in this volume by Cherniack, may be applicable to the prevention of the syndrome. In our clinic, Demerol in small doses, 25 to 40 mg. at 6-hour intervals, is preferred as a sedative since in this dosage unaccompanied by other sedatives it does not depress the respiration and functions as a bronchodilator as well. If mental confusion or somnolence begin during the program outlined above, caffeine sodium benzoate is employed, 0.5 to 1.0 Gm. at 4-to 8-hour intervals, or caffeine is used at 8-hour intervals with benzedrine, 20 mg. intramuscularly, during the alternate 4-hour period as effective drugs for stimulating an increased ventilation. The mechanical methods of augmenting the volume of breathing may also be used as additional aids in the prevention of respiratory acidosis. It is, to our mind, a serious mistake in judgment to withdraw oxygen, or to give it intermittently, in these cases, since the respiratory center is further damaged by hypoxia as well as the function of the heart and the lungs.

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An increase in the carbon dioxide tension of the arterial blood inevitably follows oxygen therapy if the pulmonary ventilation and, consequently, the dyspnea are decreased, but this retention of CO_2 is not necessarily alarming unless the pH of the blood is changed toward the acid side. A small shift in pH as a result of CO_2 retention may be followed by mental changes if it takes place rapidly. The comatose state is not, therefore, called carbon dioxide narcosis in our clinic, but respiratory acidosis. Frequently, a very considerable degree of carbon dioxide retention is found prior to oxygen treatment as a result of impaired diffusion plus the administration of sedatives. It is not commonly recognized that the *arterial blood CO_2 may be lowered as a result of oxygen treatment.* Following the initial rise, for example, from an arterial CO_2 content of 65 to 85 or 90 volumes per cent during a 3-week period of oxygen treatment, the carbon dioxide may gradually fall to 70 volumes per cent and then later, during inhalation of air, to 60 volumes per cent. This reduction in blood CO_2 is not produced artificially by mechanical hyperventilation but takes place as a result of improvement of the function of the lungs and therefore better diffusion of CO_2.

The fall in blood carbon dioxide during oxygen therapy seems to me to offer crucial evidence in this respect. In Fig. 6 and Fig. 7, data from the studies of Richards and the author reveal the decrease in arterial CO_2 content in a patient with pulmonary fibrosis and cardiac insufficiency, respectively. It will be seen that the initial rise in carbon dioxide, accompanying the relief of dyspnea and decrease in ventilation, was followed by a decrease in CO_2 during continuation of oxygen therapy as the vital capacity of the lungs increased; in the patient with cardiac failure, the compensatory elimination of chlorides, precipitated by the early rise in carbon dioxide, played a role in the diureses that is often a characteristic response of oxygen therapy, especially marked in cases with pulmonary emphysema and right or left heart failure. The pCO_2 in this case fell from 40 to 36 mm. Hg *during oxygen treatment,* with the pH not significantly altered, or slightly elevated.

The clinical results of oxygen treatment in pulmonary emphysema include a progressive diminution in the volume of breathing, a prompt lowering of the pulse rate, with a diuresis in cases of cardiac insufficiency, a decrease in alveolar distention, and a remarkable diminution in expectoration. Whether this is due to a cessation of the hypoxic influence on capillary permeability or to a diminution in the previously existent locally applied excessive negative pressures during inspiration, or to some other cause, the fact itself is an indication that bronchial constriction has been alleviated. Physiologically based measures that aid diffusion of oxygen and carbon dioxide, which in themselves improve the bronchopulmonary function, are preferable to mechanical ventilation; these measures include the use of prednisone, antibiotic therapy, bronchodilator aerosols, and medication by drugs during the period of oxygen treatment.

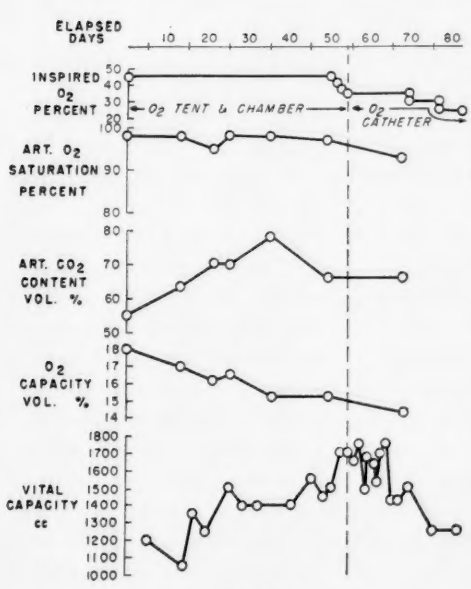

Fig. 6.

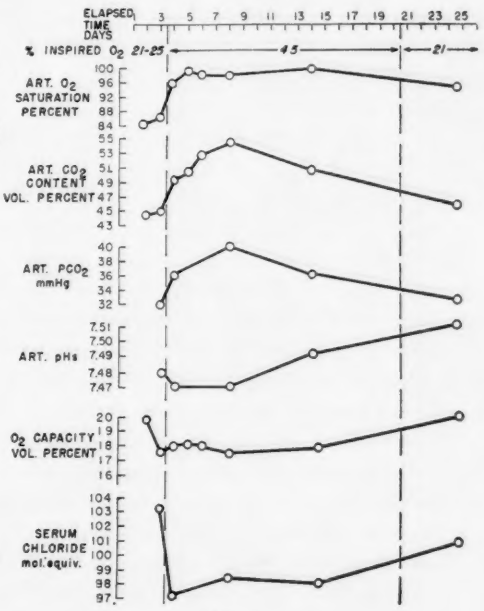

Fig. 7.

Fig. 6.—Decrease in arterial CO_2 content, following an initial use, produced during oxygen therapy in a patient with pulmonary fibrosis. Improvement in respiratory function revealed by rise in vital capacity.

Fig. 7.—Decrease in arterial pCO_2 following an initial rise in a patient with cardiac insufficiency during continous oxygen therapy, with compensatory fall in chlorides. (Data from Richards, D. W., Jr., and Barach, A. L.: Quart. J. Med. 24:437, 1954).

It has been emphasized that the presence of high CO_2 concentrations in the blood has created undue alarm since it has not been understood by some writers on this subject that a high alveolar CO_2 also allows the patient to take advantage of the lower pulmonary ventilation engineered by inhalation of oxygen because the higher partial pressure of CO_2 facilitates diffusion of the gas into the alveoli. The expired carbon dioxide is not as high as it might be because of inadequate ventilation of some of the alveoli, especially in bullous areas of

the lung, but the homeostatic nature of the retention of CO_2, although initially caused by organic disease, is of sufficient importance to warrant additional discussion. Arbitrary efforts to lower the elevated blood CO_2 in the absence of a true respiratory acidosis, manifested by pH change, have the disadvantage of destroying this mechanism. The patient then, on exercise, may rapidly develop increased CO_2 retention with acid shift in pH because the buffer bicarbonate reserve was previously lowered by a hyperventilation program. In my opinion, the employment of hyperventilation devices is not indicated, except in cases with a true respiratory acidosis. This view is not, however, held by some of the advocates of I.P.P.B. Thus, Fishman, Samet, and Cournand have not apparently been impressed by the adaptive changes described by Richards and the author over a period of many years, nor by a similar point of view expressed by Christie and Riley, but appear to believe that "the action of increased CO_2 tension is a depressant of physiologic and mental processes, which occasionally progresses to the stage of narcosis and death."

These authors further state that the compensatory elevation of CO_2 would result in a lowering of the arterial pO_2 while breathing CO_2-free air. However, in the large number of cases with a normal or nearly normal arterial oxygen saturation, the effect of the drop in pressure due to increased pCO_2 is small indeed, because of the relatively flat shape of the dissection curve of hemoglobin in this range. The calculation of the effect produced is made on the basis of the formula referred to in the discussion of altitude hypoxia. Thus 760—47 (water vapor) = 713, the inspired air pressure, 713 × .21 (oxygen per cent in the atmosphere) = 150, the inspired oxygen pressure. Deducting 40 mm. Hg for the alveolar pCO would give 110 mm. Hg; if the alveolar pCO_2 was elevated to 50, the alveolar oxygen pressure would be 100 mm. Hg, which would have an insignificant effect in these cases of pulmonary emphysema. In instances in which the alveolar pCO_2 rises to 60 to 80 mm. Hg during oxygen therapy, the alveolar pO_2 is raised by the increased concentration of the inhaled atmosphere and, therefore, offsets the dilution factor of an increased tension of carbon dioxide. In severe hypoxia the steep slope of the dissociation curve accounts for the fact that administration of even low concentrations of oxygen, i.e., 28 per cent, results in a relatively large increase in arterial oxygen concentration (cf. Fig. 2). The adaptive chemical changes in the arterial blood were indeed originally reported in hypoxic patients who were tested by oxygen therapy. In summary, granted that a rise in pCO_2 of from 40 to 60 mm. will decrease the pO_2 from 110 to 90, assuming an R.Q. of 1, this 20 mm. fall in O_2 could be fully compensated (under normal conditions) by an increase of 3 per cent in the oxygen concentration of the inspired air. A 1 per cent increase at sea level is equivalent to a 7.13 change in inspired pO_2. Naturally, in pulmonary emphysema the increase in inspired oxygen would be somewhat higher to produce a similar increase in oxygen absorbed into the arterial blood.

Comroe has, in fact, recently confirmed our finding of an adaptive mechanism in a case history reported in a panel discussion by Cullen and co-workers, as follows:

> Patients with pulmonary disease who develop CO_2 retention over a long period of time seem to get along pretty well. Dr. Francis Wood had a patient at the University Hospital who was kept alive for a year or two by the use of nasal oxygen. We meas-

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ured his arterial pCO_2 at different times during that period of 2 years; it increased from 60 mm. of mercury to 85, and then to 140 mm. of mercury and stayed there for a year or more. During all this time he was alert, jolly, and even quite witty, so he certainly was not narcotized.

Therefore, over long periods of time, there must be some compensation so that over long periods of time people can tolerate very high tensions without any gross damage.

It is of considerable interest that the cerebral blood flow was found to be markedly elevated as a result of inhalation of oxygen and the accompanying rise in arterial CO_2 tension in 6 or 9 cases reported by Patterson, Heyman, and Duke. Sudden changes in oxygen tension, both above and below that to which the individual is accustomed, may in themselves play a role in alterations in mental function in addition to the effect of a respiratory acidosis and alkalosis. In a case of hypoventilation associated with encephalitis that we reported in 1920, inhalation of 80 per cent oxygen for one and one-half hours produced a rise in arterial CO_2 content from 64 to 88 volumes per cent as the arterial oxygen saturation rose from 60 to 84 per cent. Had mechanical hyperventilation procedures been employed at that time to prevent a CO_2 acidosis, the cerebral blood flow would presumably not have been elevated; at any rate the indication for prevention of abrupt carbon dioxide retention is now clear in any case in which diminished volume of respiration is present.

The secondary increased excretion of chlorides as a result of elevation of CO_2 after oxygen therapy was also shown to play a role in the initiation of a diuresis in cases of cardiorespiratory failure. This response seemed to be in part responsible for restoration of compensation in some cases of congestive heart failure that were refractory to other measures.

In the accompanying roentgenogram (Fig. 8) the response of a man 66 years of age with pulmonary emphysema and clinical evidence of right and left heart insufficiency is shown before and after oxygen therapy and bi-weekly injections of Mercuhydrin. The interlobar effusion cleared and the size of the heart decreased on this combined therapy; dyspnea was relieved within several hours after inhalation of approximately 40 per cent oxygen was begun, even though previously resistant to bed rest and digitalis. Increased rest and sleepiness were clinically evident as effects of the therapeutic program, which ultimately resulted in restoration of circulatory compensation. Irrationality was not provoked by oxygen therapy but drowsiness was present for four days, in all probability the consequence of CO_2 retention and a slight or moderate fall in pH, although no measurements of the arterial blood gases were made.

It should be emphasized that it is not oxygen therapy that is dangerous, but rather an unwarranted curtailment of oxygen therapy. In these cases of severe hypoxia a small increase in alveolar oxygen results in a relatively large increase in arterial oxygen saturation, because of the steep slope of oxygen dissociation curve. During the past twenty years confused mental states have been encountered at times, but infrequently when the program of gradual increase and gradual lowering of the oxygen concentration delivered to the patient has been followed, with the precautions mentioned above. If indeed stupor does take

Fig. 8.—Following three weeks of continuous inhalation of 40 per cent oxygen and biweekly injections of Mercuhydrin the heart size was markedly diminished and the fluid in the pleural space between the right middle and lower lobes cleared.

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place when low oxygen concentrations are employed, sedatives should be withheld or counteracted by drugs which stimulate the ventilation; the indication is certainly to continue treatment.

The oxygen tent is the most comfortable method of administering oxygen as well as a hygienic atmosphere produced by the air conditioning units now available. If the injector of the Meter mask is employed through a separate opening into the tent canopy, low concentrations of oxygen may be given without accumulation of carbon dioxide and with small oxygen flows. Thus, at a meter setting of 40 per cent, 1 liter of oxygen passing through the meter into the tent draws with it 3.14 liters of air. If the guage is set at 6 liters per minute, the total air-oxygen mixture entering the tent is 25 liters per minute. The actual oxygen concentration in the tent at this setting is in practice between 30 and 33 per cent because of additional leakage under the canopy; the CO_2 in the tent atmosphere is below 1 per cent. There are meters available with a larger orifice in the injector which provides 32 per cent oxygen. At an oxygen flow of 4 liters the air-oxygen mixture passing through the meter into the tent is 28 liters per minute, i.e., 6 liters of air to 1 of oxygen. Because of leakage the tent atmosphere is less, 25 to 27 per cent. Since the air-conditioned tent is more comfortable than the nasal catheter, it can be used with the method outlined above. It should be realized that the replacement of the air atmosphere with an air-oxygen mixture must have sufficient volume to dilute the carbon dioxide concentration below 1 per cent. In Leonard Hill's bed tent, oxygen was blown across the subject's face for this purpose but no provision was made to keep the tent atmosphere itself hygienic in terms of the heat, moisture, or carbon dioxide given off by the patient. In our early development of the ventilated oxygen tent, calcium chloride and soda lime were used, but, later, cooling coils were substituted for cooling and de-humidification. The suggestion of Rosenbluth and Block to dispense with soda lime by increased oxygen flows was adopted; but it must be understood that a patient with fever may have a CO_2 production of 300 c.c. per minute which would require an entrance into the tent, either by leakage or an injector, of 30 liters per minute. The claim made at times that a tent, hood, or face tent will provide 50 per cent oxygen at a flow of 6 to 8 liters per minute without undue accumulation of carbon dioxide cannot be substantiated. Thus, 8 liters of O_2 plus 22 liters of air will dilute the CO_2 to 1 per cent in cases with a CO_2 production of 300 c.c. per minute, but the oxygen concentration of the combined air-oxygen mixture of the inhaled atmosphere is 28 per cent.

For intelligent, conscious patients, the canopy employed has an inside as well as an outside zipper so that the patient can release himself if necessary when the nurse is not present, such as when he needs to go to the bathroom in a hurry. The inside zipper often provides a feeling of mental security in that the patient has less of the sensation of claustrophobia; if anything dire should happen, he would be able to leave the tent by himself through the large opening provided. The tent with the meter attached and the new canopy is illustrated in Fig. 9.

The injector meter is also used in connection with the administration of oxygen with the closed head tent. The latter device, used mainly for nebulizing

watery or detergent aerosols, is not so comfortable as either the air-conditioned cabinet with the enlarged canopy that covers the entire bed or the more recently introduced small portable oxygen tent.

Fig. 9.—The photograph illustrates the inside zipper opening which permits the patient to release himself when indicated and also the attachment with two injector meters, by which either 33 to 40 per cent oxygen or 45 to 70 per cent oxygen can be administered. At the 33 per cent meter setting, 6 liters per minute of oxygen results in a total flow into the tent of 42 liters of 32 per cent oxygen; at a 40 per cent meter setting 10 liters per minute of oxygen results in a total flow of 41 liters of 40 per cent oxygen. The actual concentration of oxygen in the tent is generally 5 per cent below the meter setting.

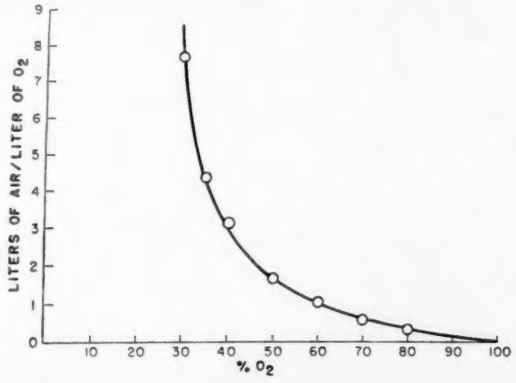

Fig. 10.—The chart illustrates the increased quantity of air drawn into the injector at low meter oxygen settings. Thus, to obtain a total flow above 30 liters per minute, 5 liters per minute of oxygen would draw 30 liters of air, or a total of 35 liters, at a 32 per cent oxygen setting. At a 40 per cent setting 9 liters of oxygen would draw 28 liters of air resulting in a total flow of 37 liters per minute. These calculations are of interest in respect to the amount of air oxygen flow required to dilute the CO_2 given off by the patient; in addition, high inspiratory pressures in pressure breathing devices may be aided by high flows of gas into the mask.

In Fig. 10 the volume of air delivered into a tent, hood, or a mask at different oxygen settings of the injector is presented. It will be seen, for example, that 1 liter of oxygen will draw in twice as much air at 32 per cent as at 40 per cent oxygen.

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OXYGEN INHALATION DURING WALKING EXERCISE

In 1951 two patients with pulmonary emphysema in whom dyspnea on exertion was markedly relieved during inhalation of oxygen were reported by Barach, Bickerman, and Beck; this response served as a basis for instituting an exercise program that resulted in a marked improvement in pulmonary reserve in some of these cases, as manifested by subsequent increased capacity for moderate exertion breathing air. The method employed consisted of the inhalation of 8 to 10 liters per minute of oxygen through the double plastic nasal tubes, by which approximately 40 to 43 per cent oxygen is provided in the inspired air, while the patient strode back and forth across the room. The substantial improvement that takes place at times seems to be due to an increase in circulatory efficiency as well as in general physical findings. The emphasis placed by Rappaport, Mayer, and other writers on lack of physical training as a cause of shortness of breath appears to be well borne out by the favorable responses of these patients to exercise during inhalation of oxygen.

Although the program is modified to the individual case, walking 50 to 100 steps with the nasal tube in place at an oxygen flow of 10 liters is generally feasible, with the addition of 100 steps daily until the patient takes 500 to 1,000 steps two or three times each day. The patient is encouraged to take half the number of steps, breathing air each day unless undue dyspnea develops. When a progressive improvement in ability to walk with lessened dyspnea takes place, after a period of a month or two, it has been presumed that a physiologic response, similar to the effect of the training program in athletes, has been produced. It has been apparent that the rise in pulse rate after walking is considerably less following an adequate period of exercise with oxygen than at the onset of treatment although no correlation could be found with the measurement of the vital capacity.

In a study of 240 patients with chronic diffuse obstructive emphysema by Miller, Fowler, and Helmholtz, the arterial oxygen saturation was found to be normal in half of this group, even after exercise. Twenty-three per cent had hypoxemia at rest, and the additional 27 per cent developed hypoxemia during a standard exercise test. Although the incidence of hypoxemia was reported to be greater in patients with more marked clinical disability, the presence or absence of hypoxemia did not govern the degree of disability in individual cases. Cor pulmonale with congestive failure occured almost exclusively in patients who had either transient or persistent hypoxemia. These findings are of considerable interest especially in view of our observation that the majority of patients with pulmonary emphysema reveal a significant reduction in pulmonary ventilation during the inhalation of 100 per cent oxygen, whether the arterial oxygen saturation is lowered, nearly normal, or normal.

Our conclusion has been that these patients maintain an augmented volume of breathing, even though it is burdensome, with the result that the arterial oxygen saturation is thereby restored toward the normal level and, furthermore, that inhalation of oxygen is manifestly a highly significant factor in the reduction of dyspnea. Our data tends to support the view that in cases in which the pulmonary ventilation is immediately reduced by inhalation of 100 per cent oxygen, benefit

will be derived from the oxygen exercise program outlined above. There are, unquestionably, instances in which the relief of dyspnea achieved by inhalation of oxygen is inadequate to support exercise, especially in advanced cases and those with pulmonary fibrosis as well. However, a considerable number of patients, encouraged to overcome the inertia so frequently present in this entity, have recorded both subjective and objective improvement. It is of interest to report that in two cases in which the program was abandoned for three months, a return to dyspnea on slight exertion was manifested; in each instance subsequent utilization of the oxygen exercise program was followed by increased well-being and increased capacity for exertion.

Quantitative tests of cardiac and pulmonary function are not available to support the clinical impression described above, except for the observation that the pulse rate, even after a short period of two or three weeks' exercise during inhalation of oxygen, does not rise as high as was observed during the control tests. Among the difficulties of interpreting pulmonary function tests and their alteration by a long-term program is the fact that a steady state can rarely be achieved, since ups and downs in the patient's condition spontaneously take place and numerous other therapies are so frequently altered during the period of observation. Nevertheless, it seems reasonable to state the following: (1) exercise increases the cardiopulmonary reserve of normal individuals exposed to suitable training programs; (2) lack of physical fitness is characteristic of middle-aged and older people; (3) patients with pulmonary emphysema are especially prone to loss of physical fitness because of their tendency to dyspnea on slight exertion; (4) many patients with pulmonary emphysema are enabled to perform a walking exercise during inhalation of 8 to 10 liters per minute of oxygen in relative comfort and without shortness of breath; (5) the continued use of an oxygen exercise program in some of these cases is followed by evidence of improved cardiopulmonary reserve, as manifested by less dyspnea and a decrease in tachycardia on exertion.

The technique of making this type of exercise possible has consisted in the use of a 50 foot length of rubber tubing attached to a high pressure oxygen cylinder and regulator. A small portable three-wheel truck has also been used which contains a G cylinder holding 320 liters of oxygen and a handle by which the patient can push the truck up and down the hospital corridor. A small oxygen regulator is used to which is attached a 4-foot length of rubber tubing to connect with a double bent nasal catheter or plastic nasal tube. A still smaller regulator has been used with the G cylinder or with a 8-pound carry-around oxygen bottle suspended from the shoulder, containing 160 liters of oxygen. A modification of this cylinder is being studied, which may be more conveniently carried on the back.

At a flow of 8 liters per minute the large oxygen cylinder commonly in use would provide more than twelve hours of walking exercise. The smaller cylinders may be employed in the hospital, by an oxygen therapy company, or if desired, by the patient himself with the use of three large cylinders connected with a manifold. For patients who carry out this program at home, the large oxygen cylinder with the 50 foot length of rubber tubing is the least expensive. The double bent plastic tubes or nasal catheters are more comfortable than any

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other form of oxygen therapy for this purpose; however, if higher concentrations are desired to accomplish more relief of dyspnea, as setting of 50 to 60 per cent with the Meter mask, especially with expiratory positive pressure of 2 to 4 cm. H_2O, may be used with an oxygen flow of 15 liters per minute.

Masks are employed to administer oxygen in intermittent concentrations between 50 to 100 per cent, for the treatment of severe hypoxia, for aerosolization of bronchodilator aerosols with the nebulizer attached to it, and for the joint use of oxygen and aerosols with expiratory pressure breathing. The Meter mask has several important advantages over the B.L.B. mask. Carbon dioxide in the collecting rubber bag is kept below 0.2 per cent even at low oxygen flows by means of an inspiratory valve. Oxygen concentrations of 45 to 100 per cent may be accurately administered by the setting on the injector. The mask can be operated to provide concentrations of oxygen between 33 and 40 per cent at low oxygen flows, i.e., 4 to 6 liters per minute, with minimal resistance and without building up of CO_2. The carbon dioxide in the rebreathing bag of the B.L.B. apparatus at these rates of oxygen delivery varies between 1.5 to 2.5 per cent, which manifestly is undesirable in patients with emphysema. The intermittent inhalation of oxygen by mask for periods of 15 minutes three or four times a day has been used to relieve dyspnea, reduce pulmonary distention, or overcome the so-called oxygen debt that may be present in hypoxic cases; a concentration between 40 and 60 per cent is generally adequate.

CLINICAL APPLICATION OF PRESSURE BREATHING

The clinical use of continuous pressure breathing was introduced in 1935 to aid the mechanics of breathing primarily through its effect on the respiratory passageway and on the circulation. No significant increase in arterial oxygen tension would be expected as a result of the physical effect of the increased pressure since the alveolar oxygen po_2 would be elevated less than 1 per cent at sea level with the use of 5 to 7 mm. Hg mean mask pressure, in contrast to the gain mentioned earlier of 2,500 feet when 15 mm. Hg was used to overcome hypoxia at a 40,000 feet altitude.

The immediate reaction to breathing through a constricted orifice is an increase in the intrapleural negative pressure during inspiration and a decreased negativity in an intrapleural pressure in expiration. In animals subjected to prolonged experimental tracheal obstruction, the inspiratory intraplural negative pressure increases progressively, with the end result that marked congestion at the bases of the lungs produces severe hypoxia. The inhalation of oxygen then results in a decrease in the volume of breathing and a corresponding drop in intrapleural negative inspiratory pressure. When a mixture of 80 per cent helium and 20 per cent oxygen is inhaled during the early phase of the experiment, the intrapleural negative pressure during the inspiratory cycle is decreased because of the physical laws governing effusion or turbulent flow. If air is breathed at this time under a continuous positive pressure of 5 to 6 cm. H_2O, an almost proportionate reduction in the inspiratory negative pressure in the intrapleural cavity was found, and, as a consequence of inspiratory flow being physically facilitated, a consistent

decrease in the volume of breathing took place. We also observed in one of our patients with severe status asthmaticus that the inspiratory intrapleural negative pressure was reduced 4 cm. H_2O by continuous pressure respiration with an 80 per cent helium and 20 per cent oxygen mixture.

The effort of breathing during the inspiratory cycle is relieved by pressure breathing primarily because of this decrease in the negative pressure required for inflation of the lungs. The maintenance of a positive pressure during expiration involves the added use of the abdominal and intercostal muscles to expel the inhaled air, which has no adverse effect on the respiratory system but, as shown by Barach and Swenson, had the physiologic advantage of increasing the diameter of the smaller bronchi in patients with bronchial asthma and thereby decreasing obstructive dyspnea. Other studies have since revealed that increased lung volume and bronchial dilatation are characteristic consequences of pressure breathing. An additional advantage of pressure breathing, suggested by Comroe, is that the lengthening of the bronchial tree may decrease distorted curving of the bronchioles.

Pressure breathing was also employed clinically as a measure of critical value in acute pulmonary edema due to left ventricular failure or to changes in permeability in the pulmonary epithelium occuring in pneumonia and gas poisoning. Effective control of edema has been produced with expiratory pressure, continuous and inspiratory intermittent pressure breathing. The mechanism through which improvement takes place includes the factors discussed above, but in the main the benefit is linked to the increased pooling of blood in the peripheral vascular system, manifested, as revealed in the studies of Barach, Martin, and Eckman, by a characteristic rise in venous pressure; thus, in normal individuals about 40 per cent of the applied intrapulmonary pressure was found by these authors to be counterbalanced by a comparable rise in arm venous pressure; in pulmonary congestion due to cardiac insufficiency the venous pressure rose considerably higher, 60 per cent or more, depending on the degree to which the lungs and chest wall absorbed the remainder of the applied pressure. The pulmonary capillaries, in our opinion, were presumably constricted by the increased pulmonary pressure, decreasing the tendency for serum to escape into the alveoli. The effect of pressure breathing varies with the degree of pressure applied and the state of the circulation, but it tends to retard the inlet of blood into the right auricle and thereby enables the heart to pump more effectively with a smaller volume, an advantage in cases of pulmonary emphysema with either left or right heart failure, as well as in cases of "cardiac asthma" (paroxysmal passive pulmonary congestion) and pulmonary edema.

Intermittent positive pressure breathing, originally employed for resuscitation, and later, during World War II, for overcoming altitude hypoxia, was used by Motley, Gordon, Theodos, and others in conjunction with continuous nebulization of bronchodilator aerosola in the treatment of patients with pulmonary emphysema. The value of intermittent pressure breathing itself depends primarily on the principles described above in the application of continuous positive pressure breathing; in addition, the I. P. P. B. devices in current use increase the pulmonary ventilation, which is beneficial when indicated for the treatment of respiratory acidosis.

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Intermittent positive pressure breathing employed as an adjunct to the continous nebulization of aerosols of the bronchodilator type will be discussed by Fowler, Helmholtz, Miller, and Bickerman. However, a critical re-evaluation of the principles involved in its therapeutic application is also pertinent to this discussion. A statement is commonly made to the effect that the rapid fall in expiratory pressure with I. P. P. B. produces a high-velocity expiratory gas flow which promotes bronchial drainage. In comparative studies on exsufflation, which will be presented by Beck, no physical effect on the movement of bronchial secretions was evident with the relatively slow expiratory volume flow rates achieved with the use of I. P. P. B. apparatus. In order to move mucus, either clinically, in experimental studies on dogs, or in artificial lung apparatus, the velocity of air flow must be in the neighborhood of that produced by the human cough to produce a demonstrable physical effect. The fact that the patient frequently expectorates bronchial secretions after a treatment appears to be due to the dilatation of the bronchi accomplished by epinephrine and the consequent freeing of the mucus from the bronchial wall, since I. P. P. B., when employed without nebulizing drugs, does not produce this effect.

The statement that I. P. P. B. may cause cardiac embarrassment or should not be used in cardiac failure also requires clarifying comment. Motley, Cournand Werko, Dresdale, Himmelstein, and Richards, in studies on intermittent positive pressure breathing, showed that cardiac output was less impaired when the expiratory pressure curve showed a rapid rather than a gradual fall. This result may be explained, at least in large part if not entirely, by considering the slope of the pressure curve as a function of the mean applied pulmonary pressure, as indicated by earlier studies reviewed by Barach, Fenn, Ferris, and Schmidt, and more recently investigations of Maloney, Whittenburger and associates, Beck, and Barach, on the effect of various types of pressure on the venous return. The effect of the mean pressure depends not only on its degree but manifestly also on the state of the circulation. In perpiheral circulatory failure, entrance of blood into the right heart is already handicapped and a substantial increase in intrapulmonary pressure may be followed by more severe cardiac failure. On the other hand, in cases of cardiac insufficiency, the decrease of blood entering into the heart may itself result in an increased cardiac output, i.e., 10 to 35 per cent (Motley, Cournand, Werko, et al.). This response appeared to be due to a decrease in filling pressure of the right auricle, permitting the ventricle to empty more completely, and correlates well with McMichael's study of cardiac output in heart failure in which the application of tourniquets to the extremities diminished the venous return and increased the cardiac output, in accordance with Starling's law of the heart. However, in right heart failure, cardiac insufficiency may be aggravated by I. P. P. B., as indicated by the studies of Miller, Fowler, and Helmholtz.

In reviewing the literature published between 1936 and 1950, Bickerman and Beck collected sixty-four cases in which positive pressure breathing had been employed for pulmonary edema or obstructive dyspnea. Of these, twenty-eight were in pulmonary edema due to acute left ventricular failure; fourteen suffered from status asthmaticus or obstructive dyspnea; thirteen had pulmonary edema

secondary to respiratory depression; six were patients with an extensive pneumonic process, one had lung edema due to chlorine gas inhalation, and two cases followed tracheotomy. These authors reported three additional patients in whom the application of continuous pressure breathing was followed by the disappearance of lung edema. It is, therefore, precisely because of the increased mean positive pressure supplied by I. P. P. B., or any other form of supra-atmospheric pressure breathing, provided an optimal pressure is employed, that the function of the failing heart may be improved, as has been observed clinically.

An undue elevation in intrapulmonary pressure has produced the syndrome of peripheral circulatory failure; at high altitudes, where a mean pressure of 15 mm. Hg was employed, the subjects at times collapsed after a needle was put into the artery for purposes of testing the oxygen saturation. The pain, presumably associated with a fall in peripheral venous pressure, aggravated the damming-back effect of the high intrapulmonary pressures, and the arterial blood pressure then fell. The method proposed in 1938 of determining whether or not the degree of positive pressure administered was excessive, consisted of determining whether the arterial blood pressure fell unduly during treatment; an injurious degree of continuous (or mean) pressure was suspected when the arterial blood pressure decreased 15 mm. Hg or more. Although this test may not be the only or the best method of estimating the presence of an unfavorable effect on the circulation, it has appeared to be in our experience a feasible and reliable guide. Other simple measurements of the physiologic effect of pressure breathing in an individual patient included the rise in venous pressure above the control value, which revealed the degree of pressure passed on to the peripheral circulation, since a small rise occurred in subjects with normal lungs and a marked increase in cases with congestive failure, in which the elasticity of the lungs was impaired and, therefore, did not expand and absorb more of the applied pressure. If the chest and abdomen were completely restricted from an increase in volume by a pressure vest, the venous pressure rise was then 100 per cent of the applied intrapulmonary pressure; i.e., all the applied pressure was transmitted to the peripheral venous system.

The circulation time was also employed as a simple method of determining the effect of pressure breathing, since it was only slightly prolonged with a mean pressure of 6 cm. H_2O in normal individuals, and markedly prolonged, i. e., 50 to 100 per cent in patients with cardiac insufficiency. Bickerman and Beck found that the cardiac impact was reduced as a result of continuous pressure breathing at 6 cm. H_2O; as estimated by the ballistocardiograph, the reduction in calculated "cardiac output" was, in most instances, proportional to the mean applied pressure.

Other alterations that have been recorded as a result of pressure breathing include a rotation of the heart, with an increased vertical diameter of the chest, a consequent depression of the T-wave of the electrocardiogram, an increase in hematocrit and total proteins as a result of hemoconcentration.

The relation of the volume of the lung to the applied intrapulmonary pressure was studied by Fenn and his collaborators, and by others who will be referred to in reference to the studies on compliance in the chapters by Alexander and Day-

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mon. In respect to the clinical application of inspiratory pressure, a significant factor that warrants consideration is the duration of the inspiratory pressure in augmenting lung and tidal volume. Thus, in our studies with the exsufflator a peak positive pressure of 20 mm. Hg with a 2.5 second inspiration produced the same tidal volume as a peak pressure of 40 mm. Hg achieved in 1.6 seconds. Since the hazard of tearing of an emphysematous bleb is directly related to the increase in lung volume rather than the pressure itself, it became evident that the duration of pressure should not be so sufficiently prolonged as to result in undue pulmonary distention. With the use of exsufflation with negative pressure (E. W. N. P.) an abrupt termination of inspiratory pressure, from plus 20 to 40 mm. Hg peak pressure to a 40 mm. Hg negative pressure in 0.02 second, resulted in a mean mask pressure actually lower than that commonly found with a 15 mm. Hg inspiratory pressure, either as employed in a tank respirator or in intermittent pressure breathing devices. Graphic records on a Statham Strain Gauge of the character of mask pressure curves of various I. P. P. B. apparatus with E. W. N. P. revealed that the expiratory phase consumed one second or more in I. P. P. B. apparatus in contrast to a duration of positive expiratory pressure of 0.02 second with E. W. N. P. With the employment of negative pressures in expiration the mean pressure can be maintained at atmospheric level or below the atmosphere depending upon the length of the negative pressure cycle.

The importance of employing a negative pressure phase in mechanical respirators to maintain a low mean pressure and thereby prevent peripheral circulatory failure was emphasized by Maloney, Whittenberger, and others. Birnbaum and Thompson reported some years ago that inspiratory lung inflating pressures followed by expiratory negative pressures had favorable effects on the circulation of deeply anesthetized dogs that were not achieved by supra-atmospheric intermittent pressure breathing. It is of interest to note that mouth-to-mouth insufflation, an efficient form of inspiratory intermittent pressure breathing, was first employed as a medical procedure by Tossach in 1743. However, biblical records provide an even earlier example of successful application of this kind of pressure as a therapeutic agent; Elisha revived the son of a Shunamite woman who had apparently been dead for some time by putting his lips over those of the child's and breathing his spirit into the lungs of his spiritual patient.

It was noted during World War II that the application of continuous pressure breathing to overcome altitude hypoxia increased the volume of breathing in the minority of cases, whereas intermittent pressure breathing consistently resulted in more marked hyperventilation. The use of I. P. P. B. has therefore been correctly applied to patients with respiratory acidosis until the pH has been brought to the normal level. However, as previously discussed, decreasing the elevated CO_2 tension so commonly present in cases of pulmonary emphysema to a lower level is not advantageous in our experience if the arterial pH is normal.

When patients with bronchial asthma or pulmonary emphysema breathe under a continuous pressure of 4 to 8 cm. H_2O, dyspnea is generally relieved. Despite the fact that the functional residual air is increased which in itself calls for increased ventilation, measurement of the minute volume of breath-

ing is at times lowered. In addition to the physical aid to inspiration, C.P.P.B. presumably results in a better diffusion of oxygen and carbon dioxide because of the widened diameter of the smaller bronchi maintained during the expiratory cycle. With the joint use of continuous pressure of 6 cm. H_2O and the head-down position, the pulmonary ventilation is markedly lowered as compared to the record obtained sitting errect. Stimulation of proprioceptive reflexes is probably of little importance in this connection. Richards takes a similar position in respect to the heightened ventilation found in cardiac failure: "The increased tachypnea and hyperpnea in advanced heart failure raises again the question of reflex factors in lungs, great vessels or elsewhere, but again the marked and consistent relief obtained by oxygen therapy brings us back to a basic chemical control. Cardiac asthma, sometimes truly asthmatic in form, is still basically an acute pulmonary congestion. While it may respond to bronchodilators, it relief more often depends upon the use of oxygen, frequently with positive pressure, upon digitalization, sedation, and diuretics."

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The tank respirator is commonly employed for the purpose of maintaining artificial respiration in cases of respiratory paralysis due to poliomyelitis and other neurologic diseases. Although it has also been employed in the treatment of hypoventilation in patients with pulmonary emphysema, there is always the hazard that the patient's cycle of breathing may not coincide with that of the apparatus, as will be discussed by Cherniack in the treatment of respiratory acidosis. It is pertinent to this discussion to point out that intermittent pressure breathing, accomplished by the production of negative pressure surrounding the body in the tank respirator, produced physiologic effects similar to those achieved by intermittent pressure breathing, with positive pressure applied to the upper respiratory passageway by a mask or the dome of the respirator, provided that the shape and mean pressure of the ventilatory curve are comparable. Although this view has been contested by some investigators, recently by Bancroft and Wilkes, comparative studies on both types of intermittent positive pressure breathing revealed similar changes in the volume of breathing and the venous return, according to the investigations of Maloney, Whittenberger, and others, which were, in my opinion, satisfactorily confirmed in our clinic by Beck and associates.

Continuous positive pressure breathing of 5 to 8 cm. H_2O may be carried out in the tank respirator by the use of a blower that maintains a constant negative pressure in the body compartment of 5 or 8 cm. of water. Pressure breathing maintained in this way, as well as in the helium-oxygen hood, provides a comfortable and effective method of relieving obstructive dyspnea due to lesions in the tracheobronchial tree, as well as the dyspnea occurring in patients with pulmonary emphysema, bronchial asthma, and also, to a considerable extent, in cases of left ventricular failure. When the pressure is maintained with little or no fluctuation between inspiration and expiration, it is surprising to observe that patients are not aware of the effort of breathing, even during the expiratory cycle. Contrary to some reports, continuous pressure breathing is not fatiguing in clinical practice; furthermore, it frequently enables the orthopneic patient to lie supine without discomfort. In fact, intermittent pressure breathing devices that maintain a comparable mean pressure are in our experience not as subjectively pleasant to the asthmatic or emphysematous patient as C.P.P.B. with the methods outlined

above. Finally, premature bronchial closure appears to be less apt to take place in patients with pulmonary emphysema when the pressure is maintained at 6 cm. H_2O during expiration and inspiration than when it drops to the atmosphere as in I. P. P. B. The spirometric measurements in a patient with severe pulmonary emphysema, seen in Fig. 11 reveal the effect of 6 cm. when applied as negative pressure around the body enclosed in a tank respirator. It will be seen that a reduction in minute volume of breathing took place from 11.5 to 10.5 liters per minute in changing from the supine position to the supine position with a continuous positive pressure breathing of 6 cm. A further decrease to 8,700 c.c. occurred when the head-down position was combined with continuous positive pressure breathing. In the latter instance a considerable decrease in oxygen consumption took place, namely from 260 to 170 c.c. per minute. The change from costal to diaphragmatic breathing as produced by headward tilt of the thorax of 18 degrees resulted in itself in a decrease in minute volume of breathing from 11.5 to 9.4 liters.

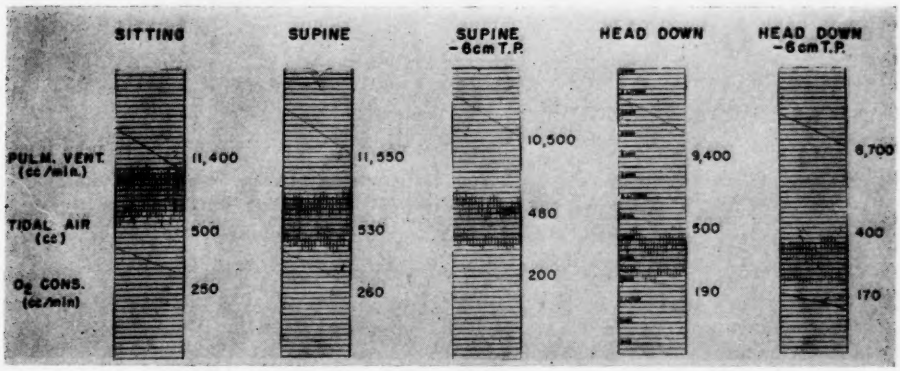

Fig. 11.—Effect of continuous positive pressure breathing in a patient with pulmonary emphysema. Continuous positive pressure breathing was obtained by providing a negative pressure of 6 cm. of water in the body compartment of a tank respirator in the supine position, the ventilation decreased from 11.5 to 10.5 liters per minute. When this pressure was exerted at a headward tilt of the thorax of 10°, the ventilation dropped further to 8.7 liters per minute. The effect of diaphragmatic breathing produced by the head-down position alone was manifested by a decrease in pulmonary ventilation from 11.5 to 9.4 liters per minute with a decrease in oxygen consumption from 260 to 190 c.c. per minute.

In 1936 when the joint effect of inhalation of 80 per cent helium with 20 per cent oxygen with 8 cm. H_2O C.P.P.B. was tested in a patient with pulmonary ventilation, the reduction in ventilation then recorded was from 15.7 to 10.6 liters per minute, a result similar to the effect of inhaling 100 per cent oxygen. The decrease in ventilation accomplished in a patient with partial obstruction of the left main bronchus yielded a similar result. As seen in Fig. 12, the pulmonary ventilation decreased from 8,560 to 6,600 c.c. when the helium oxygen mixture administered with continuous pressure breathing, was substituted for air; the ventilation with 100 per cent oxygen was 7,380 c.c. per minute.

The mask continous pressure breathing device formerly used in our clinic is not as satisfactory as a recently developed apparatus in which the elastic force of a distensible rubber bag is employed to provide an even pressure through-

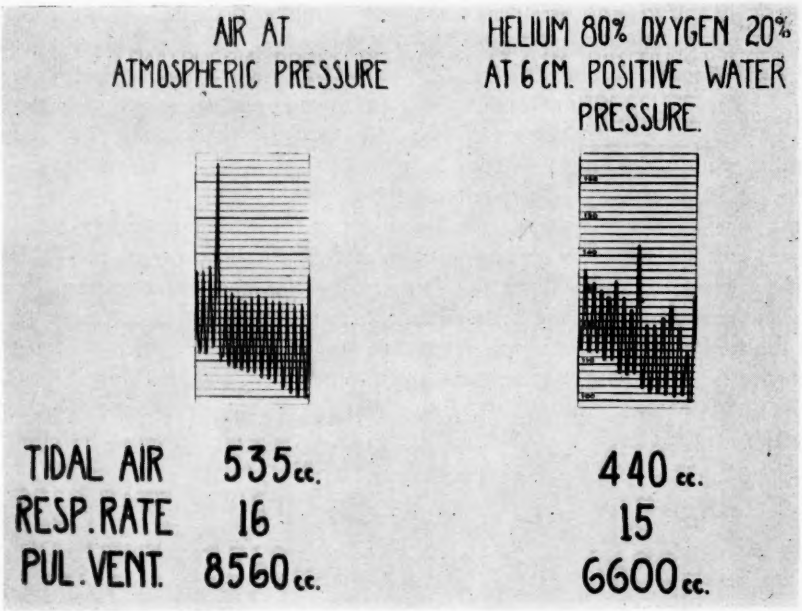

Fig. 12.—A decrease in pulmonary ventilation took place from 8,560 c.c., breathing air to 6,600 c.c. per minute when the patient breathed 80 per cent helium with 20 per cent oxygen at a continuous pressure of 6 cm. H_2O. Diagnosis: Partial obstruction of left main bronchus. (From Barach, A. L.: J. A. M. A. 107:1273, 1936).

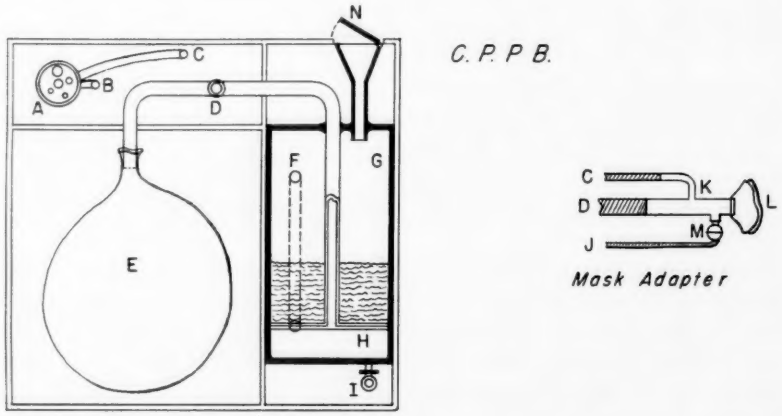

Fig. 13.—Diagram of continuous pressure breathing apparatus, indicating use of elastic rubber bag and perforated metal can as expiratory valve. *A*, Oxygen-air injector; *B*, oxygen inlet; *C*, oxygen-air outlet to mask; *D*, pressure line from pressure accumulator to mask; *E*, pressure accumulator (rubber balloon); *F*, slight gauge calibrated in centimeters of water pressure at the mask; *G*, water tight brass tank; *H*, perforated brass plate to diffuse expiratory air bubbles and reduce water level excursion; *I*, drain valve for draining tank and adjusting pressure level; *J*, oxygen to nebulizer; *K*, mask-tubing-nebulizer fitting; *L*, face piece with cushion; *M*, nebulizer for introduction of aerosols; *N*, filler pipe and air vent—open while in use, sealed when being transported.

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out the respiratory cycle. By means of an injector used at a setting of 33 per cent oxygen, an inspiratory flow of 10 liters per minute of oxygen draws into the mask an additional 60 liters of air. Expiration takes place under water through a series of small holes in a perforated metal can. It was emphasized previously that a slight increase in the inspiratory oxygen pressure results in a

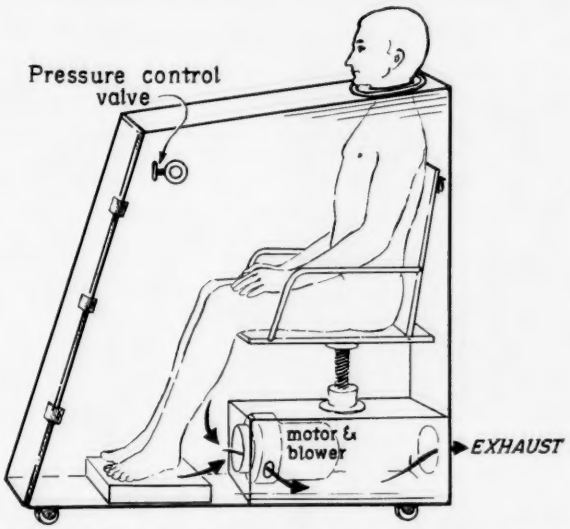

Fig. 14.—Sitting-up chamber for study of continuous positive pressure breathing maintained by maintenance of a negative pressure of 2 to 10 cm. surrounding the body.

relatively large increase in arterial oxygen saturation in severely hypoxic patients with pulmonary emphysema because of the steep slope of the oxygen dissociation curve of hemoglobin in the presence of the severe degree of oxygen want frequently found in these cases. During the administration of air with continuous pressure breathing the dyspnea is relieved as a consequence of the improved diffusion of oxygen and carbon dioxide but greater alleviation of hypoxia may be expected with the employment of either 33 or 40 per cent oxygen atmospheres. Even more complete relief of obstructive dyspnea would be provided by inhalation of 80 per cent helium with 20 per cent oxygen. With the use of the latter gas the injector is closed and the oxygen regulator set at 15 liters a minute, which would result in a flow of 26 liters of the helium-oxygen mixture. A pressure setting of 5 to 6 cm. of water may be found useful for most cases, but this can be varied to suit the needs of the individual patient. For optimal maintenance of continuous pressure a flow of not less than 7 liters per minute is required at the 33 per cent oxygen setting and 10 liters per minute at the 40 per cent setting. The continuous pressure breathing device is illustrated in Fig. 13.* A sitting-up box which positive pressure breathing may be studied through the maintenance of 5 of 8 cm. negative pressure in the body compartment is illustrated in Fig. 14.†

*Made by O. E. M. Corp., East Norwalk, Conn.
†Made by Respiration Aids. 424 East 123rd St., New York, N.Y.

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Editorials

THE PRESENT STATUS OF ANTICOAGULANTS

The leading cause of death and invalidism in persons over the age of 50 is thromboembolism. The advent of heparin and coumarin derivatives offered for the first time a means of attacking this problem directly. During the past twenty years, every conceivable type of thromboembolism has been treated with anticoagulants, or attempts at prophylaxis have been made. In some conditions the use of these drugs was disastrous, as in subacute bacterial endocarditis. In others, they have been lifesaving.

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The first disease to be attacked with heparin was subacute bacterial endocarditis in 1936. At that time, effective antimicrobial agents were not available. Heparin was given in an effort to prevent the deposit of fibrin on the bacterial vegetations. Many such patients succumbed to cerebral hemorrhage, probably from the weakening of the blood vessel walls due to the toxemia of the disease. The method immediately fell into disrepute. Subacute bacterial endocarditis has since been considered a contraindication to anticoagulant therapy. Recently this problem has been reapproached. Rheumatic heart patients who have had showers of emboli and who are maintained on continuous Dicumarol therapy as a prophylactic, occasionally develop "s.b.e." Some such patients have been continued on their Dicumarol therapy and at the same time given penicillin. Clinical cure of subacute bacterial endocarditis has resulted with no untoward effects from the Dicumarol, which in turn continued to afford protection against embolization.

Phlebitis and pulmonary embolism were the first conditions to be successfully treated. Simultaneous reports from the Mayo Clinic group[1] and Swedish workers[2] have since been confirmed in every clinic working on this subject. The mortality from subsequent pulmonary emboli can be reduced from 18 per cent to less than 1 per cent.

Thromboembolic phenomena after myocardial infarction are a major complication of this condition. The cooperative clinic study of the American Heart Association[3] showed conclusively that mortality and morbidity could be greatly reduced by the proper use of these drugs. Recently, it has been suggested that anticoagulants be reserved for "severe" cases of this disease. Myocardial infarction is notorious for masking its clinical signs and symptoms. Indeed, the diagnosis is often hidden until a major thromboembolic complication focuses attention on it. The physician at the bedside attempts to estimate, when he first sees the patient, whether the case will be severe or mild, and so decide

whether to give or to withhold anticoagulants. I believe that prognostic acumen has not been perfected to this degree and so give anticoagulants to all patients when it can be done conveniently and safely.

Following an embolus or other form of acute occlusion of an artery to a limb, the blood flow in the affected capillary bed is very sluggish. While awaiting collateral blood flow to be established, there is great danger of thrombosis in situ in the capillaries and veins of this area. This danger can often be successfully combated by the prompt use of anticoagulants. Propagation of the embolus or thrombus can also be stopped.

Cerebral vascular disease poses a challenge. Over 95 per cent of cerebrovascular accidents are due to thrombosis or embolism. Less than 5 per cent are due to hemorrhage. Where the former diagnosis can be definitely established, it seems reasonable to suppose that anticoagulants may be of value to prevent extension of the clot or the development of new emboli from fibrillating auricles. Although the first reports on this subject were published in 1950,[4] there has been little work done on this problem by other groups. It must be considered an experimental field.

Long-term therapy has been outstandingly successful in preventing emboli from fibrillating auricles. Patients have been maintained on this therapy for as long as eight years.[5] Attempts have been made to forestall threatened coronary artery thrombosis by this method. The results are suggestive but difficult to evaluate.[5,6] The most recent report by Suzman and his co-workers[7] in a review of eighty-two treated cases and eighty-eight controls shows a significant reduction in mortality during a period of from three months to six years of therapy.

The technique of administering these drugs has undergone considerable change. Heparin is now available in highly concentrated form. As much as 20,000 units may be given in 1 c.c. Such amounts may be given in a deep subcutaneous injection. Excellent anticoagulant activity may be expected, starting one hour after the injection and lasting for fourteen to twenty hours. The new preparation is not as painful and its effects are more reliable than the older forms of heparin mixed with gelatin and glucose, given intramuscularly. Unfortunately, the report of heparin activity by the sublingual route could not be substantiated. Heparin-like products, such as Paritol, have proved to be too toxic for clinical use.

The number of oral anticoagulants has greatly increased. In addition to Dicumarol, other coumarin derivatives are available. Tromexan is quicker acting and more rapidly excreted. Marcumar acts about as quickly as tromexan, but is slowly excreted. Phenylindanedione acts rapidly and is excreted quickly. It gives urine an orange tint that may be confused with hematuria. It is advisable for the physician to master the vagaries of one drug, and to use it exclusively. In long-term therapy, Dicumarol has been the drug most widely employed.

Antidotes have improved. Vitamin K_1 given orally in a dose of 20 mg. will reduce unduly elevated prothrombin times to a therapeutic level in a period of six hours. Quicker action can be obtained by intravenous injection. The preparation is an oil and has to be given in an emulsion over a period of hours. This

method, therefore, has little advantage over the oral route. The antidote to heparin is protamine. One hundred milligrams will counteract the effect of approximately 10,000 units of heparin. Whole fresh blood may be used to counteract bleeding from heparin or coumarin derivatives. Fresh blood, by direct transfusion technique, is preferred. Stored blood is not a good coagulant agent because of the anticoagulant used in collecting it.

A word of caution should be given. This therapy should only be undertaken by physicians who have mastered it. They must be willing to devote the time and effort of following each case in minute detail. A reliable laboratory must be available. Only intelligent, cooperative patients should be given long-term therapy. The patient must be tested frequently. Antidotes must always be on hand. The physician cannot take a day off or a vacation, unless the patient is attended by another physician equally skilled in the technique of this therapy. As a reward for this painstaking effort, many patients not amenable to any other form of treatment can be maintained as useful citizens.

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THE PRESENT STATUS OF ANTICOAGULANTS

In an accompanying editorial[1] and elsewhere,[2] leading proponents of anticoagulant therapy present their current views. As they have noted, however, others have expressed somewhat divergent views; a few of these are summarized in the following pages.

Differences of opinion are most apparent with respect to the routine use of anticoagulants in acute myocardial infarction. Publication of the final, monumental report[3] on the studies of the Committee on Anticoagulants of the American Heart Association has not completely allayed earlier misgivings[4] over progress reports. The point at issue is clear: inasmuch as prognosis after infarction varies so greatly under the influence of a wide variety of factors, the validity of results derived from any comparison of control with treated patients depends upon the demonstration of random selection of the two groups. That the Committee's study did not deal with patients who were actually selected at random has been pointed out elsewhere[5-7] and in fact was noted by the Committee itself.[3] The failure to obtain randomization was of a greater statistical magnitude than the reduction in case fatality rate claimed for anticoagulants,[5] so that differences in these rates were not necessarily the result of such treatment but may have arisen from chance factors.

It is, of course, possible that anticoagulation therapy rather than chance was responsible for the different case fatality rates (23.4 per cent in 442 control, and 16.0 per cent in 589 treated, patients). Evidence for this rests upon the acceptance as valid of a series of corrections[3] applied to the original observations, and here the Committee and its critics alike are on less firm ground. What, for example, is the meaning of the fact that a greater proportion of treated than control patients had private or semiprivate rooms and special nursing care? Was this nicely balanced by the greater incidence of severe cases in the treated group, or, in any event, did the treated group receive better care in addition to anticoagulants and more medicines in general? Surely such questions, distinctly subsidiary to the major one of random sampling, are open to honest differences of opinion not to be settled by statistical fiat.

The issue has been clouded somewhat by the introduction of another subsidiary question, that pertaining to the selection of only certain patients with acute myocardial infarction for anticoagulant therapy; here again unanimity is lacking.[2,8-11] Granting uncertainties in the initial evaluation of prognosis for a given individual, many acknowledge the benign course seen in the majority of "good risk" patients and therefore question the need for anticoagulants in them. At the other extreme, anticoagulants may not benefit "very poor risk" patients.[12] Perhaps they reduce the case fatality rate in "poor risk" ones, but the criteria for this category remain somewhat uncertain.

Another approach toward appropriate selection of patients involves the demonstration of accelerated coagulation of blood as an indication for anticoagulant therapy[13]; further study seems desirable. Again, it seems rational to use such therapy when cardiac infarction is impending; unfortunately, infarction is not averted in every case and indeed it is most difficult to judge whether such management is effective at all even when heparin is used.[14]

When consideration turns from that of case fatality to thromboembolic episodes, it is apparent that the latter certainly occur and may be serious even in otherwise mild cases of myocardial infarction.[2] One needs then to decide whether reduction in the incidence of these episodes by anticoagulant therapy is valuable enough to warrant the latter's hazards[15,16]; these include a two- and threefold risk of cardiac rupture and hemopericardium, respectively, as determined by one necropsy study in which it was observed incidentally that mural thrombi were not prevented.[16]

The long-term use of anticoagulants in the prevention of recurrences of myocardial infarction is giving results which seem favorable,[17] but one must agree with the view[2] that their value in this regard is not yet conclusively established. Other studies with anticoagulants in ambulatory patients over long periods of time have shown that the obvious difficulties need not be prohibitive under favorable conditions. Above all, benefit has been demonstrated most certainly by the termination of multiple embolic events in selected patients with mitral stenosis and auricular fibrillation.[18,19]

Cerebral emboli are also prevented in such a setting,[20] but the evaluation of anticoagulants in the management of classical acute cerebral thrombosis or embolism is in doubt, although there is more evidence that treatment of this sort may avert thrombosis at times.[21] Parenthetically, note should be taken of recent histologic studies[22] which question the occurrence of thrombosis as a common cause of cerebral infarction and which stand in contrast to the finding of thrombosis or embolus in 90 per cent of instances of fresh, pale infarct of the brain.[23]

In chronic congestive heart failure, lack of random selection[5] detracts seriously from the claimed value of anticoagulants in one study[24]; analysis of other reports[25-27] shows that statistically significant results were not demonstrated. Yet another author stated that anticoagulant therapy improved the death rate in myocardial infarction only if congestive failure were present.[10] In this connection, the association of thromboembolic phenomena with rapid diuresis during the management of patients with congestive failure has been established[28]; obvious therapeutic implications include the avoidance of overtreatment in such patients.

Embolism because of the successful conversion of auricular fibrillation to sinus rhythm by means of quinidine is so rare that anticoagulants are not indicated, "except perhaps in cases of repeated embolisms in the recent past."[29] It is doubtful that many clinicians would care to use anticoagulants in patients with subacute bacterial endocarditis, even though a few patients have survived this additional hazard.[1]

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Finally, there is quite general agreement concerning the value of the original anticoagulant, heparin, in acute thromboembolic episodes such as pulmonary embolism complicating venous thromboses in the legs or fresh arterial thrombosis in patients with[30,31] or without intermittent claudication. There is distinctly less agreement on the usefulness of substitutes for heparin, namely the coumarin and indandione derivatives, without preliminary administration of heparin in these episodes. In addition to the acknowledged defect inherent in their slower onset of action, one finds not only clinical impressions[17,30] but also experimental studies of which some give clear evidence of the inferiority of coumarin compounds to heparin under certain conditions.[32] The applicability of such results to man, and the relevant question as to whether human thromboses might arise from different pathogenetic mechanisms,[32,33] and thus require different anticoagulants, remain for future clarification.

Although present evidence is not conclusive, available data suggest that heparin is preferable to its substitutes in acute episodes, whereas the coumarin and indandione derivatives are not only more convenient in chronic use but seem to gain efficacy with time. It is of some interest to note the claim that these compounds when given for more than a month or so may exert a true anticoagulant action as measured by clotting time.[17] Perhaps heparin rather than its substitutes should be used in acute myocardial infarction, but this must be established by further study. Meanwhile, it would seem reasonable to distinguish sharply between heparin and other preparations in both experimental and clinical studies on the evaluation of anticoagulants.

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THE TREATMENT OF ACUTE LEUKEMIA

Acute leukemia is primarily a disease of the young. The rapid natural course, leading always to death, the weakness and pain from skeletal involvement, enlargement of lymph nodes and viscera, the massive hemorrhage into the skin, lungs, gastrointestinal tract, kidneys or brain, created a catastrophe made worse by the realization of the physician that he had nothing to offer. Until 1947, the usual treatment after verification of the diagnosis consisted of transfusion, followed by dismissal from the hospital with the prediction that death would occur within a few weeks or months, usually from massive hemorrhage or intercurrent infection.

Spontaneous remissions, averaging usually eight to ten weeks in duration, had long been observed in from 1 to 10 per cent of children with acute leukemia, usually following a bacteremia, cellulitis, or severe pneumonia. There was no specific form of treatment, although from time to time promising leads resulted in temporary encouragement to the physician, only to be followed by complete failure and disappointment.

In the latter part of 1947, a program of laboratory investigation and clinical research led to the administration of a powerful folic acid antagonist, 4-aminopteroyl glutamic acid (Aminopterin). This was followed by the production of remissions in approximately two-thirds of the children treated.[1] These remissions, when complete, were characterized by a return of the patient to a state hematologically and clinically indistinguishable from normal. This discovery initiated the era of antimetabolites in cancer chemotherapy. Doubts concerning the value of this new form of therapy for acute leukemia were expressed initially by some observers, who found that adults with acute leukemia responded poorly to such treatment, or by those who were frightened by the toxic changes produced in the mouth, gastrointestinal tract, and bone marrow resulting from too enthusiastic, improper and uncontrolled dosage. When the initial recommendations were followed accurately, uniform results were obtained in clinics in many parts of the world.[2] Aminopterin, and shortly thereafter Amethopterin (Methotrexate) are now part of the standard treatment of acute leukemia, particularly in children, producing remissions in from 60 to 90 per cent of the patients, with variations explained by the number of patients treated and the ability of the doctor or clinic to exercise constant supervision of the patient. The production of toxic changes is now regarded as a failure to suit the dose of the chemical administered to the needs and tolerance of the individual.

Late in 1949, shortly after ACTH became available for clinical investigation, a definite remission was obtained with acute leukemia by the use of ACTH alone.[3] It was soon found that cortisone, too, and later analogues of cortisone were useful antileukemic agents. Remissions are produced with the use of ACTH

or the corticosteroids in from 50 to 70 per cent of children with acute leukemia. They are of shorter duration than those produced by chemical agents.

The discovery that Aminopterin and other powerful folic acid antagonists with the amino in the 4 position had antileukemic activity encouraged research programs concerned with the discovery of other antimetabolites. The many years of synthesis and study of antipurines by Hitchings and his colleagues[4] led to the discovery of the antileukemic effect of 6-mercaptopurine.[5] Remissions are produced with 6-mercaptopurine Purinethol with as much regularity as with Methotrexate or Aminopterin, but usually they are not of as long duration. Somewhat greater effect is produced in adults than is the case with the folic acid antagonists.

The acquisition of resistance of the leukemic cells to a chemical compound or hormone to which they had once been sensitive has been encountered in the case of every one of the antileukemic agents thus far administered to man. Cross-resistance, however, has not been demonstrated. Treatment may be sequential or in the form of combinations of these chemicals or hormones. Eventually, all presently available methods fail, and death will follow a brief final period of relapse.

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In one research center,[7] almost 700 children with acute leukemia have been treated with these new anticancer agents since 1947. Survival time has been increased, in 50 per cent of the children treated, from 9 months in the folic acid antagonist period to 10 months when the corticosteroids were added, and now to 11 months since the purine antagonist could be employed either initially or subsequent to exhaustion of the value of the other agents. Encouraging also are the 10 per cent survival figures. These have increased to an average of 27½ months. A small number of children have survived for as long as 3 to 4 years. One boy has been in constant remission for 6 years and 3 months and is still in excellent health. He has been under constant treatment with a folic acid antagonist for this entire time. No evidence of toxicity has been observed at any time in response to the dose chosen for him, nor has there been any demonstrable deleterious effect upon his growth or development.

Antagonists to riboflavin, the citrovorum factor, niacin, pyridoxine, and a series of other antimetabolites derived from a number of research programs have shown effects of interest in the experimental laboratory but have so far proved to have no clinical value. Similar disappointing results in the treatment of acute leukemia have followed the trial of cytotoxic agents such as the nitrogen mustards, the phenyl butyric mustard of Haddow, the ethyleneimines, the carbamates, and antibiotics such as actinomycin C or D, although favorable effects are produced by these agents in certain forms of chronic leukemia, lymphoma, and Hodgkin's disease. The chemical compounds which have such important temporary antileukemic effects in man appear to act by preventing the synthesis of nucleoproteins, either by preventing the conversion of folic acid to the citrovorum factor or by interfering with the formation or utilization of purines.

These achievements in the treatment of acute leukemia fall short of the goal of complete cure. It they have accomplished nothing more, however, they have transformed the physician's attitude toward this as yet incurable disease. The use of these agents as part of the total care of the patient with

acute leukemia has brought not only increased survival to the patient but greater comfort and happiness to him and his family. The production of remissions and increased survival has stimulated research programs in many institutions in a number of countries. If a solution could be found to the problem of resistance of the leukemic cells to these antileukemic agents, present forms of therapy could be compared in value to insulin in the treatment of diabetes, or liver in pernicious anemia.

The search for better antileukemic agents is proceeding along empirical as well as rational approaches. Both directions must be encouraged. The likelihood is great that the cure will be found long before the exact nature or cause of leukemia will be discovered. Doctors and scientists in this field of research, impressed by the magnitude and scope of the research effort concerned with antileukemic chemicals, hormones, and antibiotics, and by the clinical achievements of the past eight years, are filled with confidence, unmarred by reference to a fickle calendar, that the cure for acute leukemia will be found.

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Book Reviews

THE PHYSICIAN AND THE LAW. By Rowland H. Long, LLB., LLM. Pg. 284; indexed. New York, 1955, Appleton-Century-Crofts, Inc. Price $5.75.

This compact work, by a prominent and experienced lawyer, is intended for physicians and medical students. Its style is clear and quite readable and the book contains much useful material. This reviewer feels that some of the contents might well have been omitted, e.g., the section advising physicians about various types of life insurance that they might purchase and the very elaborate six page outline listing every conceivable cause of sudden death. Other sections might have been expanded. Only eight pages is devoted to a presentation of psychiatry and the law. A general introductory chapter on the law, laying ground work for the medical man, would prove valuable. The author refers frequently to "common law," but no attempt is made to distinguish it from the law derived from statute and from legal decision. Nor is any clue to such knowledge to be found in the short appended glossary of legal terms.

Physicians are generally impressed with the extreme cautioness of their legal brethren. This characteristic is not painfully apparent in the case of Mr. Long. However, it seems to me that he does advise undue caution when a physician is called by the police to examine an intoxicated individual who has been injured. "If he is called upon to examine the individual as a patient who is in need of treatment, he can proceed with all the freedom granted by the rules of his profession, provided that the patient does not object to the examination. If the patient objects, the physician shall make a note that medical attention was refused and shall not examine the patient." He does seem a bit overcautious, too, when in considering deaths, "from manual strangulation or throttling" he states that "practically all of these cases are homicidal."

The author too infrequently expresses his personal view in regard to desirable changes in the law. He does forthrightly castigate trial judges for frequently permitting nonexperts to testify as qualified experts.

There are excellent and quite technical sections on blood grouping in disputed paternity cases and on bullet wounds. There is an interesting account of the Minnesota Medical Society's valuable plan to insure a high quality of medical testimony. In this book, by a medical layman, there are few statements to which one can take exception on medical grounds. It seems inaccurate to characterize glaucoma as an infrequent disease. Nor, in the reviewer's knowledge, is it necessary for a committing physician to "diagnose" the psychiatric condition; he has generally merely to assert that the patient is in need of commitment because of a mental disease and is not required to diagnose the type of insanity.

All in all, this is a valuable book and can serve well as a handy reference work.

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